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(54) Title: SUBSTITUTED 8-ARYLQUINOLINE PHOSPHODIESTERASE-4 INHIBITORS

(57) Abstract: Novel substituted 8-arylquinolines represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein S_1, S_2 and S_3 are independently H, -OH; halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein the alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH; R_1 is a H, OH, halogen, carbonyl, or -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkal) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-aryloxy, -C_1-C_6alkoxy, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl); A is CH, C-ester, or C-R_4; R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, -CN, -C_1-C_6alkyl, heterocycloC_{3-6}alkyl, -C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), aryloxy, -heteroaryloxy, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl); one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted; when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system; are PDE4 inhibitors.

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TITLE OF THE INVENTION

SUBSTITUTED 8-ARYLQUINOLINE PHOSPHODIESTERASE-4 INHIBITORS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention is directed to compounds that are substituted 8-arylquinolines. In particular, this invention is directed to substituted 8-arylquinolines which are phosphodiesterase-4 inhibitors wherein the aryl group at the 8-position contains a substituent substituted-alkenyl group.

RELATED BACKGROUND

Hormones are compounds that variously affect cellular activity. In many respects, hormones act as messengers to trigger specific cellular responses and activities. Many effects produced by hormones, however, are not caused by the singular effect of just the hormone. Instead, the hormone first binds to a receptor, thereby triggering the release of a second compound that goes on to affect the cellular activity. In this scenario, the hormone is known as the first messenger while the second compound is called the second messenger. Cyclic adenosine monophosphate (adenosine 3', 5'-cyclic monophosphate, "cAMP" or "cyclic AMP") is known as a second messenger for hormones including epinephrine, glucagon, calcitonin, corticotrophin, lipotropin, luteinizing hormone, norepinephrine, parathyroid hormone, thyroid-stimulating hormone, and vasopressin. Thus, cAMP mediates cellular responses to hormones. Cyclic AMP also mediates cellular responses to various neurotransmitters.

Phosphodiesterases ("PDE") are a family of enzymes that metabolize 3', 5' cyclic nucleotides to 5' nucleoside monophosphates, thereby terminating cAMP second messenger activity. A particular phosphodiesterase, phosphodiesterase-4 ("PDE4", also known as "PDE-IV"), which is a high affinity, cAMP specific, type IV PDE, has generated interest as potential targets for the development of novel anti-asthmatic and anti-inflammatory compounds. PDE4 is known to exist as at lease four

isoenzymes, each of which is encoded by a distinct gene. Each of the four known PDE4 gene products is believed to play varying roles in allergic and/or inflammatory responses. Thus, it is believed that inhibition of PDE4, particularly the specific PDE4 isoforms that produce detrimental responses, can beneficially affect allergy and inflammation symptoms. It would be desirable to provide novel compounds and compositions that inhibit PDE4 activity.

A major concern with the use of PDE4 inhibitors is the side effect of emesis which has been observed for several candidate compounds as described in C.Burnouf et al., ("Burnouf"), *Ann. Rep. In Med. Chem.*, 33:91-109(1998). B.Hughes et al., *Br. J.Pharmacol.*, 118:1183-1191(1996); M.J.Perry et al., *Cell Biochem. Biophys.*, 29:113-132(1998); S.B.Christensen et al., *J.Med. Chem.*, 41:821-835(1998); and Burnouf describe the wide variation of the severity of the undesirable side effects exhibited by various compounds. As described in M.D.Houslay et al., *Adv. In Pharmacol.*, 44:225-342(1998) and D.Spina et al., *Adv. In Pharmacol.*, 44:33-89(1998), there is great interest and research of therapeutic PDE4 inhibitors.

International Patent Publication WO9422852 describes quinolines as PDE4 inhibitors.

A.H.Cook, et al., *J.Chem. Soc.*, 413-417(1943) describes gamma-pyridylquinolines. Other quinoline compounds are described in Kei Manabe et al., *J.Org. Chem.*, 58(24):6692-6700(1993); Kei Manabe et al., *J.Am. Chem. Soc.*, 115(12):5324-5325(1993); and Kei Manabe et al., *J.Am. Chem. Soc.*, 114(17):6940-6941(1992).

Compounds that include ringed systems are described by various investigators as effective for a variety of therapies and utilities. For example, International Patent Publication No. WO 98/25883 describes ketobenzamides as calpain inhibitors, European Patent Publication No. EP 811610 and U.S. Patent Nos. 5,679,712, 5,693,672 and 5,747,541describe substituted benzoylguanidine sodium channel blockers, U.S. Patent No. 5,736,297 describes ring systems useful as a photosensitive composition.

U.S. Patent Nos. 5,491,147, 5,608,070, 5,622,977, 5,739,144, 5,776,958, 5,780,477, 5,786,354, 5,798,373, 5,849,770, 5,859,034, 5,866,593, 5,891,896, and International Patent Publication WO 95/35283 describe PDE4

inhibitors that are tri-substituted aryl or heteroaryl phenyl derivatives. U.S. Patent No. 5,580,888 describes PDE4 inhibitors that are styryl derivatives. U.S. Patent No. 5,550,137 describes PDE4 inhibitors that are phenylaminocarbonyl derivatives. U.S. Patent No. 5,340,827 describes PDE4 inhibitors that are phenylcarboxamide compounds. U.S. Patent No. 5,780,478 describes PDE4 inhibitors that are tetra-substituted phenyl derivatives. International Patent Publication WO 96/00215 describes substituted oxime derivatives useful as PDE4 inhibitors. U.S. Patent No. 5,633,257 describes PDE4 inhibitors that are cyclo(alkyl and alkenyl)phenyl-alkenyl (aryl and heteroaryl) compounds.

However, there remains a need for novel compounds and compositions that therapeutically inhibit PDE4 with minimal side effects.

SUMMARY OF THE INVENTION

The present invention is directed to novel substituted 8-arylquinolines that are PDE4 inhibitors, wherein the aryl group at the 8-position is substituted by a substituted-alkenyl group. This invention also provides a pharmaceutical composition which includes an effective amount of the novel substituted 8-arylquinoline and a pharmaceutically acceptable carrier. This invention further provides a method of treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic

neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues by the administration of an effective amount of the novel substituted 8-arylquinoline or a precursor compound which forms *in vivo* the novel substituted 8-arylquinoline.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a chemical schematic drawing of the general structure of the compounds of the present invention.

Fig. 2 is a graph of Counts against °Theta for an X-ray Powder Diffraction of the Form A polymorph of the benzenesulfonic acid salt of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(*E*)-2-[3-methyl-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline.

Fig. 3 is a graph of Counts against °Theta for an X-ray Powder Diffraction of the Form B polymorph of the benzenesulfonic acid salt of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(*E*)-2-[3-methyl-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline.

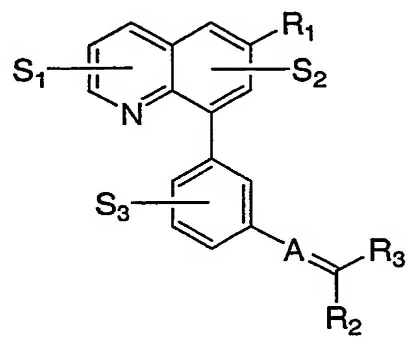
Fig. 4 is a comparison of the X-ray Powder Diffractions of the Form A polymorph (bottom trace) and the Form B (upper trace) of the benzenesulfonic acid salt of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(*E*)-2-[3-methyl-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline.

Fig. 5 is a graph of the distinguishing feature peaks of the X-ray Powder Diffraction of the Form A polymorph of the benzenesulfonic acid salt of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(*E*)-2-[3-methyl-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline.

Fig. 6 is a graph of the distinguishing feature peaks of the X-ray Powder Diffraction of the Form B polymorph of the benzenesulfonic acid salt of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(*E*)-2-[3-methyl-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline.

DETAILED DESCRIPTION OF THE INVENTION

A compound of this invention is represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein the alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a H, OH, halogen, carbonyl, or -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-aryloxy, -C_1-C_6alkoxy,

-(C_0-C_6alkyl)(C_0-C_6alkyl)amino, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH, C-ester, or C-R_4;

R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, –CN, -C_1-C_6alkyl, heterocycloC_{3-6}alkyl, -C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), aryloxy, -heteroaryloxy, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system;

R_4 is an aryl, -C_1-C_6alkyl, heteroaryl, –CN, carbonyl, carbamoyl, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a carbonyl, -CN, halogen, -C(O)(C_0-C_6alkyl), -C(O)O(C_0-C_6alkyl), -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -OH, C_1-C_6alkoxy, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, group;

n is independently 0, 1, or 2; and

R_2 or R_3 may optionally be joined to R_4 by a bond to form a ring.

In one aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein the alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a H, OH, halogen, carbonyl, or -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-aryloxy, -C_1-C_6alkoxy, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, –CN, -C_1-C_6alkyl, heterocycloC_{3-6}alkyl, -C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -heteroaryloxy, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2.

In one embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein the alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a -C_1-C_6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl), -(C_0-C_6alkyl)(C_0-C_6alkyl)amino;

A is CH;

R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, –CN, -C_1-C_6alkyl, heterocyloC_{3-6}alkyl,-C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -O-aryl, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system;

n is independently 0, 1, or 2.

In another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a -cycloC_3-C_6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, –CN, -C_1-C_6alkyl, heterocycloC_{3-6}alkyl,-C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -O-aryl, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a -C_1-C_6alkenyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, –CN, -C_1-C_6alkyl, heterocyloC_{3-6}alkyl,-C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -O-aryl, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system;

n is independently 0, 1, or 2.

In another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a heteroaryl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, –CN, -C_1-C_6alkyl, heterocyloC_{3-6}alkyl,-C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system;

n is independently 0, 1, or 2.

In still another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a an -amino, -C_1-C_6alkylamino, or -(C_1-C_6alkyl)(C_1-C_6alkyl)amino group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 and R_3 independently is an aryl, heteroaryl, H, halogen, –CN, -C_1-C_6alkyl, heterocycloC_{3-6}alkyl,-C_1-C_6alkoxy, carbonyl, carbamoyl, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH,

-C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system;

n is independently 0, 1, or 2.

In an embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -carbamoyl, -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally

substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

R_3 is a heteroaryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl); and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a halogen, carbonyl, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -carbamoyl, -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, $-NO_2$, -C(O)OH, carbonyl, -CN, $-C_1$-C_6alkyl, $-SO_n$-(C_1-C_6alkyl), $-SO_n$-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, $-C_1$-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, $-NO_2$, -CN, $-SO_n$-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

R_3 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, $-NO_2$, -C(O)OH, carbonyl, -CN, $-C_1$-C_6alkyl, $-SO_n$-(C_1-C_6alkyl), $-SO_n$-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, $-C_1$-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, $-NO_2$, -CN, $-SO_n$-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl); and

n is independently 0, 1, or 2.

In still another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, $-C_1$-C_6alkyl, $-NO_2$, -CN, or $-C_1$-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a halogen, carbonyl, $-C_1$-C_6alkyl, -cycloC_3-C_6alkyl, $-C_1$-C_6alkenyl, $-C_1$-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, $-C_1$-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, $-C_1$-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), $-SO_n$NH(aryl), $-SO_n$NH(heteroaryl),

$-SO_nNH(C_1-C_6alkyl)$, $-C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl)$, $-NH-SO_n-(C_1-C_6alkyl)$, $-SO_n-(C_1-C_6alkyl)$, -carbamoyl, $-(C_1-C_6alkyl)-O-C(CN)$-dialkylamino, or $-(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl)$ group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), $-C(O)-O-(C_0-C_6alkyl)$, -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or $-SO_n-(C_1-C_6alkyl)$;

A is CH;

R_2 is a carbonyl, optionally substituted with 1 substituent, wherein the substituent is an, aryl, heteroaryl, -C(O)OH, carbonyl, $-C_1-C_6alkyl$, -O-aryl, -O-heteroaryl, $-O-(C_1-C_6alkyl)$, -heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or $-(C_0-C_6alkyl)(C_0-C_6alkyl)$amino, substituent group, wherein each substituent group independently is optionally substituted with -OH, $-O(C_1-C_6alkyl)$, $-C_1-C_6alkyl$, -cycloC_3-C_6alkyl, -O(aryl), -C(O)OH, $-C(O)O(C_1-C_6alkyl)$, halogen, $-NO_2$, -CN, $-SO_n-(C_1-C_6alkyl)$, -cycloC_3-C_6alkyl or $-C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl)$;

R_3 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, $-NO_2$, -C(O)OH, carbonyl, -CN, $-C_1-C_6alkyl$, $-SO_n-(C_1-C_6alkyl)$, $-SO_n-(aryl)$, -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or $-(C_0-C_6alkyl)(C_0-C_6alkyl)$amino, $-C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl)$ substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, $-C_1-C_6alkyl$, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, $-C(O)O(C_1-C_6alkyl)$, halogen, $-NO_2$, -CN, $-SO_n-(C_1-C_6alkyl)$, or $-C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl)$; and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, $-C_1-C_6alkyl$, $-NO_2$, -CN, or $-C_1-C_6alkoxy$, wherein said alkyl and alkoxy groups are optionally

substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a halogen, carbonyl, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -carbamoyl, -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 is a carbamoyl, optionally substituted with 1-2 substituents, wherein each substituent is independently a carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -C_1-C_6alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C_1-C_6alkyl), -O(aryl), -COOH, -COO(C_1-C_6alkyl), halogen, -NO_2, -CN, or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

R_3 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl); and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a halogen, carbonyl, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -carbamoyl, -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 and R_3 are each independently an aryl, optionally substituted, connected to each other by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy;

R_1 is a halogen, carbonyl, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl),

$-SO_n-(C_1-C_6alkyl)$, -carbamoyl, $-(C_1-C_6alkyl)-O-C(CN)$-dialkylamino, or $-(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl)$ group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, $-C(O)(heterocycloC_3-C_6alkyl)$, $-C(O)-O-(C_0-C_6alkyl)$, -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, $-cycloC_3-C_6alkyl$, $heterocycloC_3-C_6alkyl$, aryl, heteroaryl, carbonyl, carbamoyl, or $-SO_n-(C_1-C_6alkyl)$;

A is CH;

R_2 is a $-(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl)$, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, $-NO_2$, -COOH, carbonyl, -CN, $-C_1-C_6alkyl$, $-SO_n-(C_1-C_6alkyl)$, -O-aryl, -O-heteroaryl, $-C(O)-heterocycloC_3-C_6alkyl$, $-NH-cycloC_3-C_6alkyl$, amino, -OH, or $-C_1-C_6alkyl(amino)$ substituent group, wherein each substituent group independently is optionally substituted with -OH, $-O(C_1-C_6alkyl)$, -O(aryl), -COOH, $-COO(C_1-C_6alkyl)$, halogen, $-NO_2$, -CN, or $-C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl)$;

R_3 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, $-NO_2$, -C(O)OH, carbonyl, -CN, $-C_1-C_6alkyl$, $-SO_n-(C_1-C_6alkyl)$, $-SO_n-(aryl)$, -aryloxy, -O-heteroaryl, $C_1-C_6alkoxy$, N-oxide, $-C(O)-heterocycloC_3-C_6alkyl$, $-NH-cycloC_3-C_6alkyl$, amino, -OH, or $-(C_0-C_6alkyl)(C_0-C_6alkyl)amino$, $-C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl)$ substituent group, wherein each substituent group independently is optionally substituted with -OH, $C_1-C_6alkoxy$, $-C_1-C_6alkyl$, $-cycloC_3-C_6alkyl$, -aryloxy, -C(O)OH, $-C(O)O(C_1-C_6alkyl)$, halogen, $-NO_2$, -CN, $-SO_n-(C_1-C_6alkyl)$, or $-C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl)$; and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, $-C_1-C_6alkyl$, $-NO_2$, -CN, or $-C_1-C_6alkoxy$, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a halogen, carbonyl, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -carbamoyl, -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 is a -C(O)N-(C_0-C_6alkyl)(C_0-C_6alkyl), optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO_2, -COOH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), aryloxy, -heteroaryloxy, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -C_1-C_6alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C_1-C_6alkyl), -O(aryl), -COOH, -COO(C_1-C_6alkyl), halogen, -NO_2, -CN, or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

R_3 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl); and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a halogen, carbonyl, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C_1-C_6alkenyl, -C_1-C_6alkoxy, aryl, heteroaryl, -CN, -heterocycloC_3-C_6alkyl, -amino, -C_1-C_6alkylamino, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino, -C_1-C_6alkyl(oxy)C_1-C_6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C_1-C_6alkyl), -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl), -NH-SO_n-(C_1-C_6alkyl), -SO_n-(C_1-C_6alkyl), -carbamoyl, -(C_1-C_6alkyl)-O-C(CN)-dialkylamino, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH;

R_2 is –CN;

R_3 is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), -aryloxy, -O-heteroaryl, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl); and

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein said alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is -C_1-C_6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-aryloxy, -C_1-C_6alkoxy, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH,

R_2 and R_3 each independently is an aryl or heteroaryl, wherein each is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), aryloxy, -heteroaryloxy, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2;

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S_1, S_2, and S_3 are each H;

R_1 is -C_1-C_6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl),

-C(O)-aryloxy, -C_1-C_6alkoxy, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH,

R_2 and R_3 each independently is an aryl or heteroaryl, wherein each is optionally substituted with 1-5 substituents, wherein each substituent is independently an aryl, heteroaryl, halogen, -NO_2, -C(O)OH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), aryloxy, -heteroaryloxy, C_1-C_6alkoxy, N-oxide, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2;

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-

tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "cycloalkyloxy" unless specifically stated otherwise includes a cycloalkyl group connected to the oxy connecting atom.

The term "alkoxy" unless specifically stated otherwise includes an alkyl group connected to the oxy connecting atom.

The term "aryl" unless specifically stated otherwise includes multiple ring systems as well as single ring systems such as, for example, phenyl or naphthyl.

The term "aryloxy" unless specifically stated otherwise includes multiple ring systems as well as single ring systems such as, for example, phenyl or naphthyl, connected through the oxy connecting atom to the connecting site.

Ther term "C_0-C_6alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent or a direct bond – depending on whether the alkyl is a terminus or a bridging moiety.

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC_5alkyl is a five membered ring containing from 5 to no carbon atoms.

Examples of heteroaryl include, for example, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl.

The term "heteroaryloxy" unless specifically stated otherwise describes a heteroaryl group connected through an oxy connecting atom to the connecting site.

Examples of heteroaryl(C_{1-6})alkyl include, for example, furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, oxazolylmethyl, oxazolylethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, oxadiazolylmethyl, oxadiazolylethyl,

thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

Examples of heterocycloC_{3-7}alkyl include, for example, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

Examples of aryl(C_{1-6})alkyl include, for example, phenyl(C_{1-6})alkyl, and naphthyl(C_{1-6})alkyl.

Examples of heterocycloC_{3-7}alkylcarbonyl(C_{1-6})alkyl include, for example, azetidinyl carbonyl(C_{1-6})alkyl, pyrrolidinyl carbonyl(C_{1-6})alkyl, piperidinyl carbonyl(C_{1-6})alkyl, piperazinyl carbonyl(C_{1-6})alkyl, morpholinyl carbonyl(C_{1-6})alkyl, and thiomorpholinyl carbonyl(C_{1-6})alkyl.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines.

Unless otherwise stated, the term "carbamoyl" is used to include -NHC(O)OC_1-C_4alkyl, and –OC(O)NHC_1-C_4alkyl.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, the substitution can be made at any of the groups. For example, substituted aryl(C_{1-6})alkyl includes substitution on the aryl group as well as substitution on the alkyl group.

Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and

pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric,

succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are benzenesulfonic, citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) corticosteroids, iv) H1 receptor antagonists, v) beta 2 adrenoceptor agonists, vi) COX-2 selective inhibitors, vii) statins, viii) non-steroidal anti-inflammatory drugs ("NSAID"), and ix) M2/M3 antagonists. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Creams, ointments, jellies, solutions, or suspensions containing the compound of Formula I can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.001mg/kg to about 140mg/kg of body weight per day are useful in the treatment of conditions such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid,

bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues which are responsive to PDE4 inhibition, or alternatively about 0.05mg to about 7g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01mg to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 2.5g per patient per day. Further, it is understood that the PDE4 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 0.01mg to about 1000mg of the active ingredient, typically 0.01mg, 0.05mg, 0.25mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration

such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers

are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a

compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

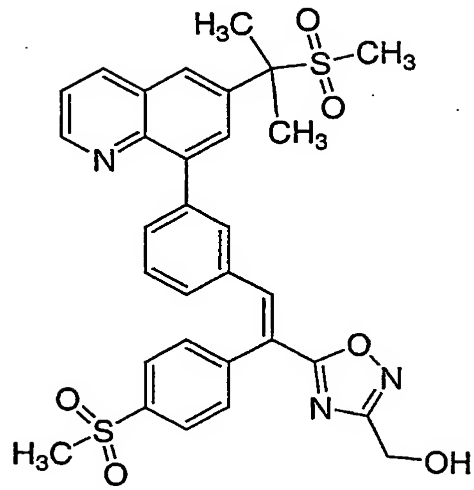
In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as PDE4 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease,

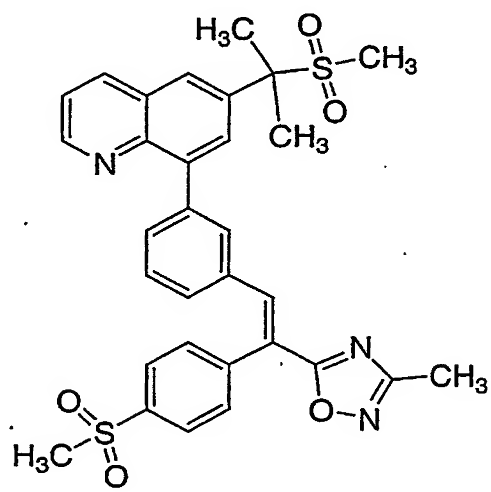
hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues – maladies that are amenable to amelioration through inhibition of the PDE4 isoenzyme and the resulting elevated cCAMP levels – by the administration of an effective amount of the compounds of this invention. The term "mammals" includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the combinations of the PDE4 inhibiting compound of this invention can be advantageously used in combination with i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) COX-2 selective inhibitors, iv) statins, v) NSAIDs, vi) M2/M3 antagonists, vii) corticosteroids, viii) H1 (histamine) receptor antagonists and ix) beta 2 adrenoceptor agonist.

In another aspect, it was found that the compound of this invention can be formed as a metabolite in the mammalian system. For example, Example 19, (5-{(E)-2-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl}-1,2,4-oxadiazol-3-yl)methanol:



which is a PDE4 inhibitor is formed *in vivo* as a metabolite when Example 14:



is administered. Accordingly, the present invention includes prodrugs that form PDE4 inhibitors *in vivo* as a metabolite after administering such prodrugs to a mammal. Further, this invention includes a method of treatment by a step of administering a prodrug to form *in vivo* an effective amount of a PDE4 inhibitor described by Formula I.

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

Ac =	acetyl
Bn =	benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DBU =	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL =	diisobutylaluminum hydride
DMAP =	4-(dimethylamino)pyridine
DMF =	N,N-dimethylformamide
Et_3N =	triethylamine
GST	glutathione transferase
HMDS	hexamethyldisilazide
LDA =	lithium diisopropylamide
m-CPBA =	metachloroperbenzoic acid
MMPP =	monoperoxyphthalic acid
MPPM =	monoperoxyphthalic acid, magnesium salt $6H_2O$
Ms =	methanesulfonyl = mesyl = SO_2Me
Ms0 =	methanesulfonate = mesylate
NSAID =	non-steroidal anti-inflammatory drug
o-Tol =	ortho-tolyl
OXONE® =	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC =	pyridinium chlorochromate
PDC =	pyridinium dichromate
PDE	phosphodiesterase
Ph =	phenyl
Phe =	benzenediyl
PMB =	para-methoxybenzyl

Pye	=	pyridinediyl
r.t.	=	room temperature
Rac.	=	racemic
SAM	=	aminosulfonyl or sulfonamide or SO_2NH_2
SEM	=	2-(trimethylsilyl)ethoxymethoxy
SPA	=	scintillation proximity assay
TBAF	=	tetra-n-butylammonium fluoride
Th	=	2- or 3-thienyl
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic acid anhydride
THF	=	tetrahydrofuran
Thi	=	thiophenediyl
TLC	=	thin layer chromatography
TMS-CN	=	trimethylsilyl cyanide
TMSI		trimethylsilyl iodide
Tz	=	1H (or 2H)-tetrazol-5-yl
CAN		ceric ammonium nitrate
C_3H_5	=	allyl

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl

c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

LPS AND FMLP-INDUCED TNF-α AND LTB4 ASSAYS IN HUMAN WHOLE BLOOD

Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE4-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF-α and LTB4. Upon stimulation with LPS, activated monocytes express and secrete TNF-α up to 8 hours and plasma levels remain stable for 24 hours. Published studies have shown that inhibition of TNF-α by increasing intracellular cAMP via PDE4 inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB4 synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE4-selective inhibitors. As there is little LTB4 produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB4 synthesis by activated neutrophils. Thus, by using the same blood sample, it is possible to evaluate the potency of a compound on two surrogate markers of PDE4 activity in the whole blood by the following procedure.

Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. 500μL aliquots of blood were pre-incubated with either 2μL of vehicle (DMSO) or 2μL of test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10μL vehicle (PBS) as blanks or 10μL LPS (1μg/mL final concentration, #L-2630 (Sigma Chemical Co., St. Louis, MO) from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10μL of PBS (blank) or 10μL of LPS (1μg/mL

final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10μL of PBS (blank) or 10μL of fMLP (1μM final concentration, #F-3506 (Sigma); diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at 4°C to obtain plasma. A 50μL aliquot of plasma was mixed with 200μL methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB_4 using an enzyme immunoassay kit (#520111 from Cayman Chemical Co., Ann Arbor, MI) according to the manufacturer's procedure. TNF-α was assayed in diluted plasma (in PBS) using an ELISA kit (Cistron Biotechnology, Pine Brook, NJ) according to manufacturer's procedure. The IC_{50} values of Examples 1-42 generally ranged from 0.04μM to 8.71μM.

ANTI-ALLERGIC ACTIVITY *IN VIVO*

Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs. Guinea pigs were initially sensitized to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminum hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later. At six weeks, animals were challenged with aerosolized ovalbumin while under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

SPA BASED PDE ACTIVITY ASSAY PROTOCOL

Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format as follows:

In a 96 well-plate at 30°C was added the test compound (dissolved in 2μL DMSO), 188mL of substrate buffer containing [2,8-^{3}H] adenosine 3',5'-cyclic phosphate (cAMP, 100nM to 50μM), 10mM $MgCl_2$, 1mM EDTA, 50mM Tris, pH 7.5. The reaction was initiated by the addition of 10mL of human recombinant PDE4 (the amount was controlled so that ~10% product was formed in 10min.). The reaction was stopped after 10min. by the addition of 1mg of PDE-SPA beads (Amersham Pharmacia Biotech, Inc., Piscataway, NJ). The product AMP generated was quantified on a Wallac Microbeta® 96-well plate counter (EG&G Wallac Co., Gaithersburg, MD). The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC_{50} value was approximated with a non-linear regression fit using the standard 4-parameter/multiple binding sites equation from a ten point titration.

The IC_{50} values of Examples 1-42 were determined with 100nM cAMP using the purified GST fusion protein of the human recombinant phosphodiesterase IVa (met-248) produced from a baculovirus/Sf-9 expression system. The IC_{50} values of Examples 1-42 generally ranged from 0.14nM to 10.24nM, although one example had an IC_{50} value of 109nM.

The examples that follow are intended as an illustration of certain preferred embodiments of the invention and no limitation of the invention is implied.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or ambient temperature - that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are

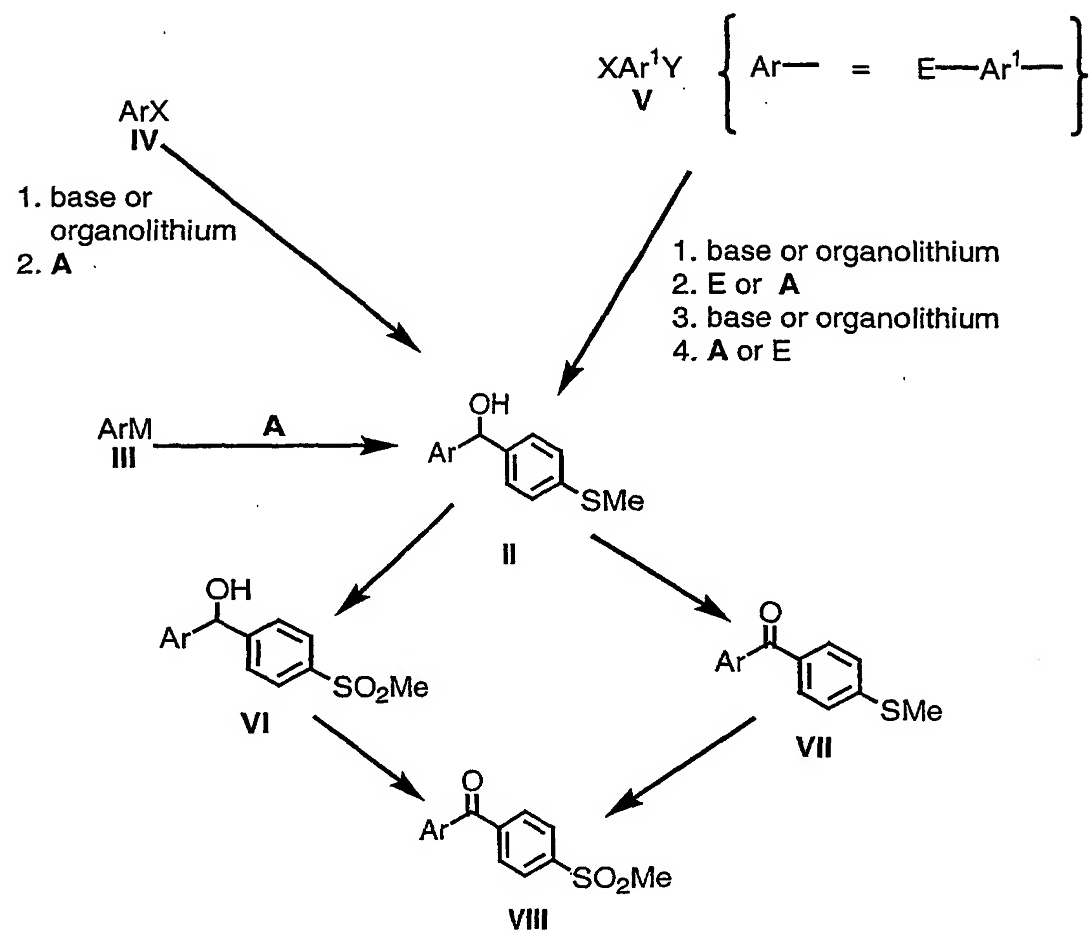
given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. Yields are given for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz, 400 MHz or 500 MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods. The substituents are the same as in Formula **I** except where defined otherwise.

SCHEME 1

Ketone Synthesis



Wherein X=halogen, H

Y=halogen, H

A=4-(methylthio)benzaldehyde

E=electrophile

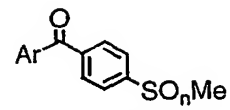
Ar=aryl or heteroaryl

Referring to Scheme 1 above, and Scheme 1 Table below, the alcohol intermediate **II** may be prepared by the reaction of an aryl or heteroaryl metallic species **III** such as an organomagnesium halide with 4-(methylthio)benzaldehyde (**A**) in an organic solvent such as THF. The alcohol intermediate **II** may also be prepared

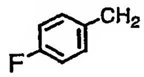
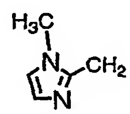
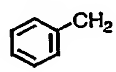
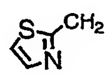
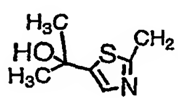
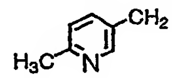
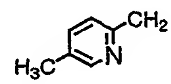
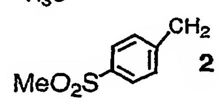
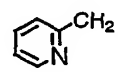
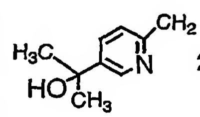
by treatment an aryl or heteroaryl hydride or bromide **IV** with a base or an organometallic such as *n*-butyllithium in an organic solvent such as THF, followed by 4-(methylthio)benzaldehyde. Alternatively the alcohol intermediate **II** may also be prepared by the following chemical transformations: 1) Treatment of an aryl or heteroaryl dihydride, halide-hydride or dihalide **V** with a base or an organometallic such as *n*-butyllithium in an organic solvent such as THF, followed by an electrophile such as acetone or 4-(methylthio)benzaldehyde; 2) Subsequent treatment with a base or an organometallic such as *n*-butyllithium in an organic solvent such as THF, followed by an electrophile such as acetone or 4-(methylthio)benzaldehyde, where the first or the second transformation must use 4-(methylthio)benzaldehyde as the electrophile. The sulfone-alcohol **VI** may be prepared by the oxidation of the sulfide-alcohol **II** with an oxidizing agent such as oxone in a solvent such as a mixture of THF/MeOH/H_2O. The ketones **VII** and **VIII** may be prepared by the oxidation of the alcohols **II** and **VI**, respectively, with an oxidizing agent such as MnO_2 in a solvent such as CH_2Cl_2. The sulfone-ketone **VIII** may also be prepared by the oxidation of the sulfide-ketone **VII** with an oxidizing agent such as oxone in a solvent such as a mixture of THF/MeOH/H_2O.

SCHEME 1 TABLE:

Ketones



VII (n=0)
VIII (n=2)

Ar	n	Ketone
	2	K1
	0	K2
	2	K3
	0 2	K4 K5
	2	K6
	2	K7
	2	K8
	2	K9
	2	K10
	2	K11

Ketone **K1**

(4-Fluorophenyl)[4-(methylsulfonyl)]phenyl ketone

Ketone K1 was prepared by the following procedure.

Step 1: (4-Fluorophenyl)[4-methylthio)phenyl]ketone

To a -78°C solution of 4-(methylthio)benzaldehyde (2.5g, 16.4mmol) in THF (100ml) was added 4-fluorophenylmagnesium bromide (1.0M in THF, 19.7ml, 19.7mmol) dropwise. The resulting solution was stirred at -78°C for 3h., and quenched with a saturated aqueous solution of NH_4Cl. The mixture was then diluted with EtOAc and HCl 10%, extracted and washed ($NaHCO_3$ (sat.), brine). The organic phase was dried over $MgSO_4$ and concentrated. The residue was then treated with MnO_2 (28.6g, 330mmol) in CH_2Cl_2 (150ml) and the reaction was stirred at r.t.

overnight. The mixture was filtered through a plug of silica (EtOAc) to yield 2.6g of the (4-Fluorophenyl)[4-methylthio)phenyl]ketone compound

Step 2: (4-Fluorophenyl)[4-(methylsulfonyl)phenyl]ketone

To a solution of the sulfide – in other words, the (4-Fluorophenyl)[4-methylthio)phenyl]ketone – from the present step 1 (2.0g, 8.1mmol) in THF/MeOH/H_2O (80/40/40 ml) was added oxone (7.5g, 12.2mmol). The mixture was stirred at r.t. for 4h, quenched with $NaHCO_3$ (sat.), and diluted with EtOAc. The organic phase was washed with $NaHCO_3$ (sat.), brine, dried over Na_2SO_4, filtered and concentrated. Crystallization (CH_2Cl_2/Hexanes) yielded (4-Fluorophenyl)[4-(methylsulfonyl)phenyl]ketone, the **K1** ketone compound, as a white solid.

Ketone **K2**

(1-Methyl-1H-imidazol-2-yl)[4-methylthio)phenyl]ketone

Ketone **K2** was prepared by the following procedure.

Step 1: (1-Methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]methanol

To a solution of N-methylimidazole (10.0g, 122mmol) in 500mL THF at -78°C was added *n*-butyllithium (2.5M in hexanes, 48.7ml, 118mmol) dropwise and the resulting solution was stirred at -78°C for 30min. 4-(Methylthio)benzaldehyde (14.73ml, 110mmol) was then added at -78°C and the mixture was stirred until completion by TLC, and quenched with NH_4Cl (sat). The mixture was then diluted with EtOAc, extracted and washed ($NaHCO_3$ (sat.), brine). The organic phase was dried over $MgSO_4$, filtered and concentrated. Crystalisation (EtOAc/Hexanes) yielded (1-Methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]methanol.

Step 2: (1-Methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]ketone

To a solution of the alcohol from the present step 1 (25.7g, 111mmol) in EtOAc (250ml) and CH_2Cl_2 (250ml) was added MnO_2 (140g, 1.66mol) and the

reaction was stirred at r.t. overnight. The mixture was filtered through a plug of silica (EtOAc) to yield ketone **K2**.

Ketone **K3**

(4-Methylsulfonyl)(phenyl)ketone

Ketone **K3** was prepared by the following procedure.

Step 1: (4-Methylthio)(phenyl)methanol

To a solution of 4-(methylthio)benzaldehyde (1.0g, 6.5mmol) in THF (20mL) at 0°C was added phenylmagnesium chloride (2M, THF, 3.5mL, 7.0mmol). After 0.5h at r.t., the mixture was neutralised with saturated NH_4Cl solution, diluted with water and extracted with Et_2O. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by stirring vigorously in hexane/Et_2O and filtration yielded (4-Methylthio)(phenyl)methanol as a white solid.

Step 2: (4-Methylthio)(phenyl)ketone

(4-Methylthio)(phenyl)ketone was obtained by treating the (4-Methylthio)(phenyl)methanol from the present step 1 with MnO_2 as in step 2 of the procedure for **K4** below.

Step 3: (4-Methylsulfonyl)(phenyl)ketone

To a solution of (4-Methylthio)(phenyl)ketone from the present step 2 (0.98g, 4.3mmol) in $CHCl_3$ (10mL) at 0°C was added mCPBA (m-chloroperbenzoic acid) (1.7g, 10mmol). After 0.5h at r.t., $Ca(OH)_2$ (1.7g, 23mmol) was added to the mixture which was stirred for 1h. Filtration on Celite® and concentration yielded ketone **K3** as a white solid.

Ketone **K4**

(1,3-Thiazol-2-yl)[4-(methylthio)phenyl]ketone

Ketone **K4** was prepared by the following procedure.

Step 1: (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]methanol

To a –78°C solution of thiazole (5.0g, 58.7mmol) in THF (250ml) was added *n*-butyllithium (2.5M in hexanes, 23.5ml, 58.7mmol) dropwise and the resulting solution was stirred at –78°C for 10min. 4-(Methylthio)benzaldehyde (7.1ml, 53.4mmol) was then added at –78°C. The resulting mixture was stirred until completion, and quenched with a saturated aqueous solution of NH_4Cl. The mixture was then diluted with EtOAc and HCl 10%, extracted and washed ($NaHCO_3$ (sat.), brine). The organic phase was dried over $MgSO_4$ and concentrated. The residue was then purified by flash chromatography (80% CH_2Cl_2/ 20% EtOAc) to yield (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]methanol.

Step 2: (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]ketone

To a solution of the (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]methanol from the present step 1 (10.0g, 42.1mmol) in EtOAc (250ml) was added MnO_2 (70g, 843mmol) and the reaction was stirred at 25°C overnight. The mixture was filtered through a plug of silica (EtOAc) to form the **K4** ketone compound.

Ketone **K5**

(1,3-Thiazol-2-yl)[4-(methylsulfonyl)phenyl]ketone

Ketone **K5** was prepared by the following procedure. To a solution of **K4** (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]ketone (8.2g, 34.7mmol) in THF/MeOH/H_2O (350/175/175 ml) was added oxone (42.6g, 69.4mmol). The reaction was stirred at 25°C for 3h and quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was then diluted with EtOAc, extracted and washed ($NaHCO_3$ (sat.), brine). The organic phase was dried over $MgSO_4$ and concentrated. The residue was then purified by crystallization (EtOAc/Hexanes) to yield of (1,3-Thiazol-2-yl)[4-(methylsulfonyl)phenyl]ketone.

Ketone **K6**

[5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylsulfonyl)phenyl]ketone

Ketone **K6** was prepared by the following procedure.

Step 1: [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylthio)phenyl]ketone

To a -78°C solution of thiazole (1.0g, 12.0mmol) in THF (100ml) was added *n*-butyllithium (2.3M in hexanes, 5.3ml, 12.3mmol) dropwise and the resulting solution was stirred at -78°C for 10min. 4-(Methylthio)benzaldehyde (7.1ml, 53.4mmol) was then added at -78°C. The resulting mixture was stirred at r.t. 10min. and cooled at –78°C. Then *n*-butyllithium (2.3M in hexanes, 5.3ml, 12.3mmol) was added dropwise and the resulting solution was stirred at 25°C for 10min and quenched with acetone (3.0ml). The mixture was then diluted with EtOAc and HCl 10%, extracted and washed ($NaHCO_3$ (sat.), brine). The organic phase was dried over $MgSO_4$ and concentrated. The residue was then treated with MnO_2 (20.4g, 235mmol) in CH_2Cl_2 (250ml) and the reaction was stirred at r.t. overnight. The resulting mixture was then filtered through a plug of silica (EtOAc). Flash chromatography (90%CH_2Cl_2/10%EtOAc) yielded [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylthio)phenyl]ketone.

Step 2: [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylsulfonyl)phenyl]ketone

To a solution of the sulfide – that is, [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylthio)phenyl]ketone – from present step 1 (1.7g, 5.8mmol) in THF/MeOH/H_2O (100/50/50 ml) was added oxone (7.1g, 11.5mmol). The reaction was stirred at 25°C for 3h and quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was then diluted with EtOAc, extracted and washed ($NaHCO_3$ (sat.), brine). The organic phase was dried over $MgSO_4$ and concentrated. The residue was then purified by crystallization (EtOAc/Hexanes) to yield ketone **K6**.

Ketone **K7**

(6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Ketone **K7** was prepared by the following procedure.

Step 1: (6-Methyl-3-pyridinyl)[4-(methylthio)phenyl]methanol

To solution of 3-bromo-6-methylpyridine (760mg, 1eq) in THF (20mL) at -78°C, was added slowly *n*-butyllithium in hexane (1.1 eq). The solution was then stirred 30min. 4-(thiomethyl)benzaldehyde (738mg, 1.1eq) was then slowly added. The solution was warmed to rt. NH_4Cl (sat.) was added, then water and EtOAc. The organic phase was separated, dried over $MgSO_4$, and concentrated. The (6-Methyl-3-pyridinyl)[4-(methylthio)phenyl]methanol was obtained by precipitation with ether/hexane and was used without further purification for the next step.

Step 2: (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]methanol

Following the procedure of step 2 of ketone **K1** above but substituting the sulfide (6-Methyl-3-pyridinyl)[4-(methylthio)phenyl]methanol from the present step 1 for (4-fluorophenyl)[4-(methylthio)phenyl]ketone as the starting material, (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]methanol was obtained.

Step 3: (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Following the procedure of step 2 of ketone **K2** above but substituting the (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]methanol from the present step 2 for (1-methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]methanol as the starting material, ketone **K7** was obtained.

Ketone **K8**

(5-Methyl-2-pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Ketone **K8** was prepared by following the procedure described for ketone **K7** but substituting 2-bromo-5-methylpyridine for 3-bromo-6-methylpyridine.

Ketone **K9**

Bis-[(4-methylsulfonyl)phenyl]ketone

Ketone **K9** was prepared by following the procedure described for ketone **K7** but substituting 4-bromothioanisole for 3-bromo-6-methylpyridine and using twice the amount of Oxone in the sulfide-oxidation step.

Ketone **K10**

(2-Pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Ketone **K10** was prepared by following the procedure described for ketone **K7** but substituting 2-bromopyridine for 3-bromo-6-methylpyridine.

Ketone **K11**

[5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]ketone

Ketone **K11** was prepared by the following procedure.

Step 1: [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylthio)phenyl]methanol

To a suspension of 2,5-dibromopyridine (5.12g, 1eq) in ether at -78°C, was added *n*-butyllithium in hexane (1.05eq) slowly. The resulting yellow-orange precipitate was strirred 30min. Then acetone (1.54ml, 1.05eq) was added. The solution was kept at -78°C for another 30min. *n*-Butyllithium in hexane (1.1eq) was slowly syringed to the resulting orange suspension. The suspension was then stirred 1h at -78°C. Following this, 4-(methylthio)benzaldehyde (2.85 ml, 1.1 eq.) was added. The resulting suspension was warmed to -35°C and quenched with a solution of NH_4Cl (sat.). Water and EtOAc were added and the organic layer dried over $MgSO_4$, evaporated and purified by flash chromatography (EtOAc) to give [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylthio)phenyl]methanol.

Step 2: [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]methanol

Following the procedure described above for step 2 of ketone **K1** but substituting the sulfide – that is, [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylthio)phenyl]methanol - from the present step 1 for (4-fluorophenyl)[4-(methylthio)phenyl]ketone as the starting material, [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]methanol was obtained.

Step 3: [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]ketone

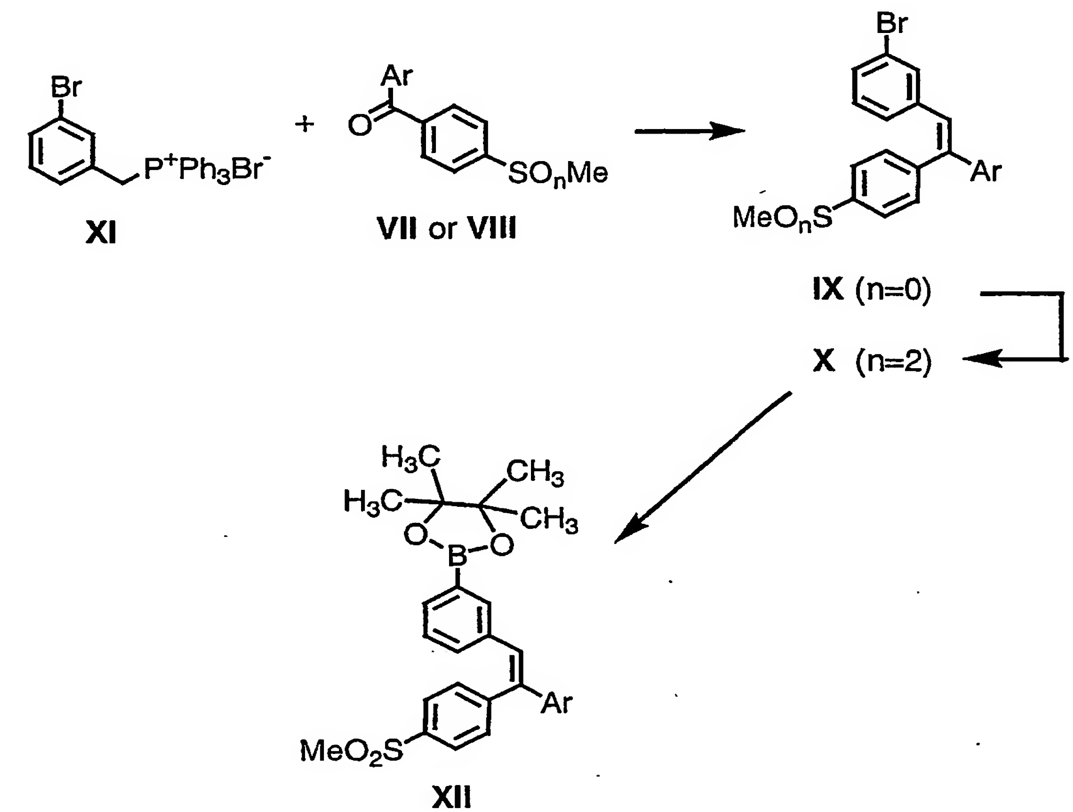
Following the procedure described above for step 2 for ketone **K2** but substituting the [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]methanol from the present step 2 for (1-methyl-1H-imidazol-

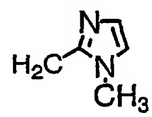
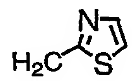
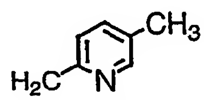
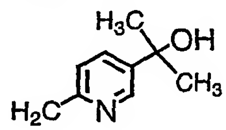
2-yl)[4-(methylthio)phenyl]methanol as the starting material, ketone **K11** was obtained.

The boronate compounds utilized to prepare the compounds of this invention can be made according to Scheme 2 shown below:

SCHEME 2

Boronate Synthesis



Ketone (VII or VIII)	Ar	n	Boronate (XII)
K2		0	B1
K4		0	B2
K8		2	B3
K11		2	B4

The aryl bromides **IX** and **X** may be prepared by treatment of the benzyl phosphonium bromide **XI** with a base such as *t*-BuOK or LiHMDS in an organic solvent such as THF, followed by the addition of the ketone **VII** or **VIII** to the reaction mixture. The sulfide in **IX** may be converted to the sulfone **X** by treatment with oxone in a solvent such as a mixture of THF/MeOH/H_2O. The boronate ester **XII** can be prepared by heating the aryl bromide **X** with pinacol diborane in the presence of a base such as KOAc and a catalyst such as $PdCl_2$(dppf) in a solvent such as DMF.

Boronate **B1**

Pinacol 3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

Boronate **B1** was prepared by the following procedure.

Step 1: (E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene

To a solution of (3-bromobenzyl)(triphenyl)phosphonium bromide (10.2g, 19.9mmol) in THF (200mL) and CH_3CN (50mL) at 25°C was added *t*-BuOK (1.0M in THF, 19.9mL, 19.9mmol) dropwise and the resulting red solution was stirred at r.t. for 20min. To this resulting ylide was then added at 25°C the ketone **K2** (4.4g, 18.9mmol). The resulting mixture was stirred at 60°C for 2 days and quenched with NH_4Cl (sat). The mixture was then diluted with EtOAc. The organic phase was washed with $NaHCO_3$ (sat.), brine, dried over $MgSO_4$, filtered and concentrated, and used directly in the next present step 2.

Step 2: (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene

To a solution of the crude sulfide – that is, (E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene – from present step 1 (18.9mmol) in THF/MeOH/H_2O (200/100/100 ml) was added oxone (23.2g, 37.8mmol). The mixture was stirred at r.t. for 4h, quenched with $NaHCO_3$ (sat.), and diluted with EtOAc. The organic phase was washed with $NaHCO_3$ (sat.), brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (95%EtOAc/5% Et_3N) yielded (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene (single isomer) as a foam.

Step 3: Pinacol 3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

A suspension of the bromide – that is, (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene – from present step 2 (2.0g; 4.8mmol), pinacol diborane (1.5g ; 5.8mmol), KOAc (1.65g; 16.8mmol) and $PdCl_2$(dppf) (0.2g; 0.24mmol) in 50mL of DMF was stirred at 90°C for 4h. The resulting mixture was cooled to r.t., diluted with EtOAc, washed with H_2O (3x), brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (95%EtOAc/5% Et_3N) yielded boronate **B1** as a foam.

Boronate **B2**

Pinacol 3-{(E/Z)-2-(1,3-thiazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

Boronate **B2** was prepared by the following procedure.

Step 1: (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylthio)phenyl]ethene

To a solution of (3-bromobenzyl)(triphenyl)phosphonium bromide (44.5g, 86.9mmol) in THF (500mL) and DMF (200mL) at 0°C was added LiHMDS (1.0M in THF, 86.9mL, 86.9mmol) dropwise and the resulting red solution was stirred at r.t. for 20min. To the resulting ylide was then added at 0°C the ketone **K4** (18.6g, 79.0mmol). The mixture was stirred until completion by TLC, and quenched with a NH_4Cl (sat). The mixture was then diluted with EtOAc. The organic phase was washed with $NaHCO_3$ (sat.), brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (CH_2Cl_2) yielded (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylthio)phenyl]ethene (1.5 to 1 mixture of isomers).

Step 2: (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene

To a solution of the sulfide – that is, (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylthio)phenyl]ethene – from present step 1 (24.8g, 63.9mmol) in THF/MeOH/H_2O (600/300/300 ml) was added Oxone (78.5g, 128mmol). The resulting reaction mixture was stirred at r.t. overnight. The resulting mixture was quenched with a $NaHCO_3$ (sat), and diluted with EtOAc. The organic phase was washed with $NaHCO_3$ (sat.), brine, dried over Na_2SO_4, filtered and concentrated to yield (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene (3 to 2 mixture of isomers).

Step 3: Pinacol 3-{(E/Z)-2-(1,3-thiazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

A suspension of the bromide (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene from present step 2 (15.0g, 35.7mmol), pinacol diborane (10.9g, 42.8mmol), KOAc (12.3g, 125mmol) and $PdCl_2$(dppf) (1.46g, 1.78mmol) in 350mL of DMF was stirred at 90°C for 4h. The resulting mixture was cooled to r.t., diluted with EtOAc, washed with H_2O (3x), brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (Tol/Acetone, 9/1) yielded boronate **B2** (3 to 1 mixture of isomers) as a foam.

Boronate **B3**

Pinacol 3-{(E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

Boronate **B3** was prepared by the following procedure.

Step 1: (E)-2-(3-Bromophenyl)-1-(5-methyl-2-pyridinyl)-1-[4-(methylsulfonyl)phenyl]ethylene

Following the procedure described for step 1 for boronate **B1** but substituting the ketone **K8** for ketone **K2** as the starting material, (E)-2-(3-Bromophenyl)-1-(5-methyl-2-pyridinyl)-1-[4-(methylsulfonyl)phenyl]ethylene was obtained after separation of the isomers by flash chromatography.

Step 2: Pinacol 3-{(E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

Following the procedure described for step 3 for boronate **B1** but substituting the bromide (E)-2-(3-Bromophenyl)-1-(5-methyl-2-pyridinyl)-1-[4-(methylsulfonyl)phenyl]ethylene from present step 1 for (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene as the starting material, boronate **B3** was obtained.

Boronate **B4**

Pinacol 3-{(E)-2-(5-(1-hydroxy-1-methylethyl)-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

Boronate **B4** was prepared by the following procedure.

Step 1: (E)-2-(3-Bromophenyl)-1-[5-(1-hydroxy-1-methylethyl)-2-pyridinyl]-1-[4-(methylsulfonyl)phenyl]ethene

Following the procedure described for step 1 for boronate **B1** but substituting the ketone **K11** for ketone **K2** as the starting material, (E)-2-(3-Bromophenyl)-1-[5-(1-hydroxy-1-methylethyl)-2-pyridinyl]-1-[4-(methylsulfonyl)phenyl]ethene was obtained after separation of the isomers by flash chromatography.

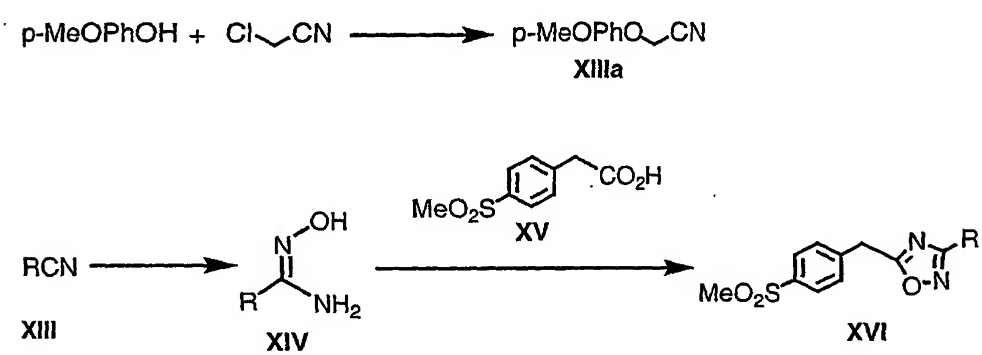
Step 2: Pinacol 3-{(E)-2-(5-(1-hydroxy-1-methylethyl)-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenylboronate

Following the procedure described for step 3 for boronate **B1** but substituting the bromide (E)-2-(3-Bromophenyl)-1-[5-(1-hydroxy-1-methylethyl)-2-pyridinyl]-1-[4-(methylsulfonyl)phenyl]ethene from present step 1 for (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene as the starting material, boronate **B4** was obtained.

The aryl bromide compounds utilized to prepare the compounds of this invention can be made according to Schemes 3 and 4 shown below:

SCHEME 3

Oxadiazole Synthesis



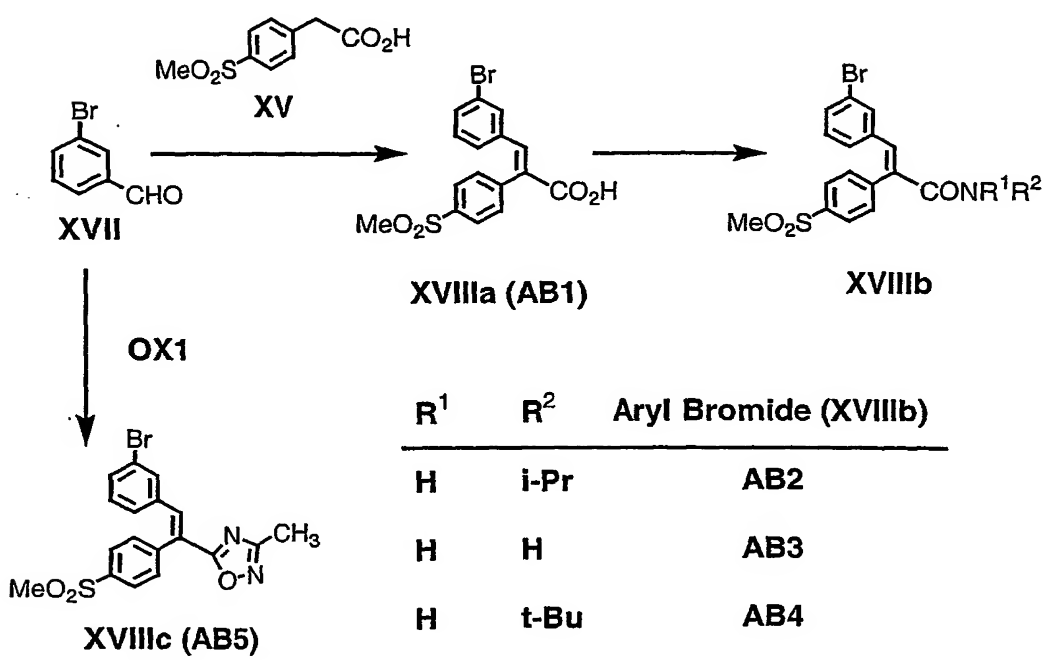
R	Oxadiazole (XVI)
Me	OX1
p-MeOPhOCH$_2$	OX2

Referring to Scheme 3 above, the nitrile intermediate **XIIIa** may be prepared by the alkylation of 4-methoxyphenol with chloroacetonitrile in the presence of a base such as potassium carbonate in a solvent such as acetone. The amide-oxime **XIV** may be prepared by treatment of the nitrile **XIII** with hydroxyl amine in a

solvent such as methanol in the presence of a base such as sodium acetate. Formation of the oxadizole **XVI** may be achieved by activation of the arylacetic acid **XV** with carbonyldiimidazole in a solvent such as DMF followed by the addition of the amide-oxime **XIV** and subsequent heating of the reaction mixture.

SCHEME 4

Aryl Bromide Synthesis



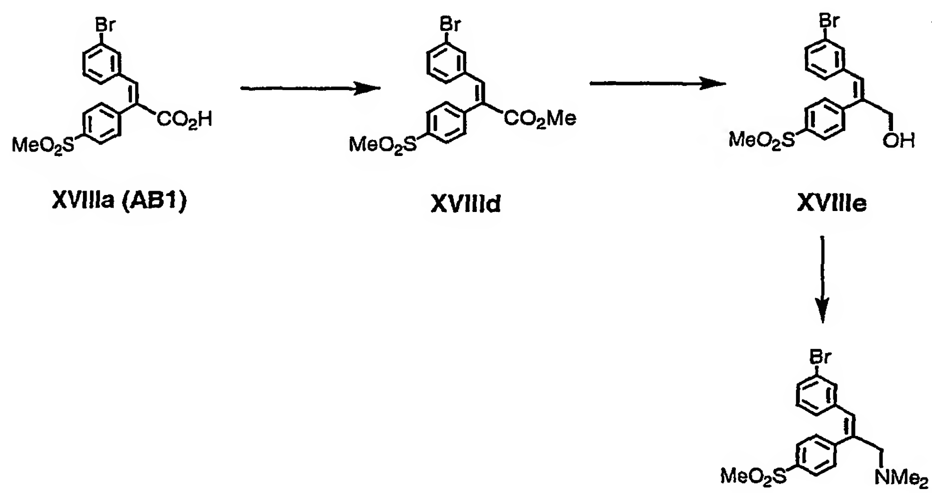
R^1	R^2	Aryl Bromide (XVIIIb)
H	i-Pr	AB2
H	H	AB3
H	t-Bu	AB4

Referring to Scheme 4 above, condensation of the aldehyde **XVII** by heating with the arylacetic acid **XV** in the presence of a base such as piperidine in a solvent such as toluene produces the unsaturated acid **XVIIIa**. Formation of the acid chloride of **XVIIIa** *in situ* by treatment with thionyl chloride and a base such as triethylamine in a solvent such as toluene, is followed by the addition of an amine to the reaction mixture to yield the amide **XVIIIb**. The oxadiazole-ethene **XVIIIc** may

be formed by heating **OX1** with **XVII** in the presence of a base such as piperidine in a solvent such as toluene.

Scheme 4 appendix

Aryl Bromide Synthesis



XVIIIf (AB6)

Referring to Scheme 4 appendix above, treatment of the acid **XVIIIa** with diazomethane in a solvent such as THF produces the methyl ester **XVIIId.** Reduction of the ester **XVIIId** using DIBAL-H in a solvent such as THF gives the allylic alcohol **XVIIIe.** Conversion of the alcohol group in **XVIIIe** to a leaving group such as a mesylate using reagents such as methanesulfonyl chloride and triethylamine in a solvent such as THF, followed by displacement with a nucleophile such as dimethylamine in a solvent such as DMF produces the compound **XVIIIf.**

Aryl Bromide **AB1**

(E)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid

Aryl Bromide **AB1** was prepared by the following procedure. To a solution of 3-bromobenzaldehyde (12.9g, 70mmol) in toluene (100mL) was added 4-(methylsulfonyl)phenylacetic acid (15g, 70mmol) and piperidine (2mL). After overnight refluxing, the mixture was cooled down to r.t. To the slurry thus formed, toluene was added (10 mL). Filtration gave (E)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid as a white solid.

Aryl Bromide **AB2**

(E)-N-Isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

Aryl Bromide **AB2** was prepared by the following procedure. To a solution of **AB1** (24.9g, 65mmol) in toluene (250mL) was added thionyl chloride (14.3mL, 196mmol) and triethylamine (34mL, 245mmol). After stirring at r.t. for 0.5h., isopropyl amine (28mL, 327mmol) was added. After a further 2h at r.t., the mixture was cooled to 0°C and was neutralised with saturated NH_4Cl solution, then extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 1:1 to pure EtOAc) yielded (E)-N-Isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide.

Aryl Bromide **AB3**

(E) -3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

Aryl Bromide **AB3** was prepared by following the procedure described for aryl bromide **AB2** but substituting ammonium hydroxide for isopropyl amine as the starting material.

Aryl Bromide **AB4**

(E)-N-(t-Butyl)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

Aryl Bromide **AB4** was prepared by following the procedure described for aryl bromide **AB2** but substituting *t*-butyl amine for isopropyl amine as the starting material.

Aryl Bromide **AB5**

(E)-1-(3-Bromophenyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethene

Aryl Bromide **AB5** was prepared by the following procedure.

Step 1 (Scheme 3, Oxadiazole **OX1**): (3-Methyl-1,2,4-oxadiazol-5-yl) [4-(methylsulfonyl)phenyl]methane

To a solution of 4-(methylsulfonyl)phenylacetic acid (15g, 70mmol) in DMF (300mL) at r.t., was added carbonyldiimidazole (12.5g, 77mmol). After 0.5h at r.t., acetamide oxime (5.7g, 77mmol) was added. After stirring the resulting mixture overnight at r.t., the mixture was heated to 120°C for 6h. After cooling to r.t., the mixture was quenched with H_2O, and extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 1:1) yielded (3-Methyl-1,2,4-oxadiazol-5-yl) [4-(methylsulfonyl)phenyl]methane.

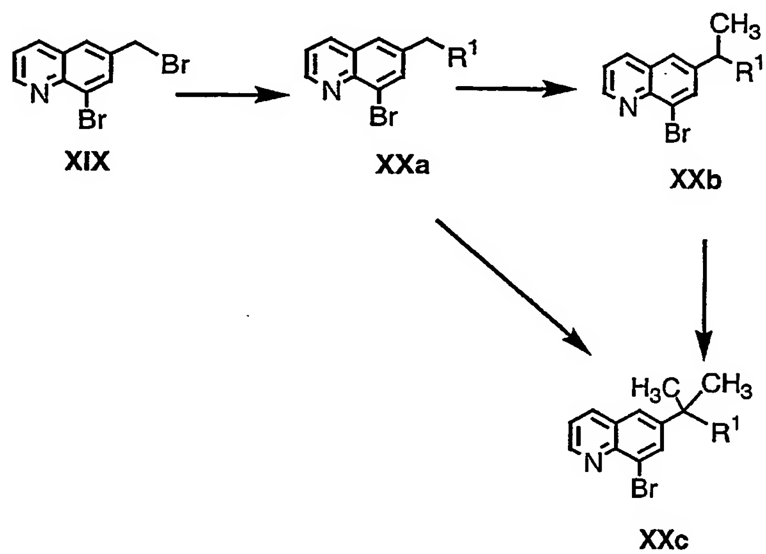
Step 2 (Scheme 4): (E)-1-(3-Bromophenyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethene

To a solution of 3-bromobenzaldehyde (2.2g, 11.9mmol) in toluene (30mL) was added the product from step 1 (**OX1**) (3.0g, 11.9mmol) and piperidine (0.4mL). After overnight refluxing, the mixture was cooled down to r.t. To the resulting slurry, MeOH (30mL) was added. After further refluxing then cooling to 0°C, filtration gave (E)-1-(3-Bromophenyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethene as a white solid.

The Bromoquinolines utilized to prepare the compounds of this invention can be made according to Scheme 5 shown below:

SCHEME 5

Preparation of Bromoquinolines

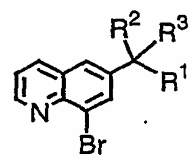


Referring to Scheme 5 above and the Scheme 5 table below, treatment of the bromomethyl compound **XIX** with a nucleophile such as sodium methanesulfinate or potassium cyanide in a solvent such as DMF or a mixture of DMF and water can be used to produce the compounds **XXa**. The compound **XXb** may be prepared by treatment of **XXa** with a base such as potassium *t*-butoxide (1.1 equivalents) in a solvent such as THF followed by the addition of the resulting mixture into a solution of methyl iodide in a solvent such as THF. The compound **XXc** may be prepared by treatment of **XXb** with a base such as potassium *t*-butoxide (1.1 equivalents) in a solvent such as THF followed by the addition of the resulting mixture into a solution of methyl iodide in a solvent such as THF. The compound **XXc** (where R^1 = CN) may also be prepared by treatment of **XXa** with a base such as potassium *t*-butoxide (2.2 equivalents) and methyl iodide in a solvent such as THF.

The compound **XXc** (where $R^1 = SO_2Me$) may also be prepared by treatment of **XXa** with a base such as potassium *t*-butoxide (1.3 equivalents) and methyl iodide (1.6 equivalents) in a solvent such as THF, followed by an additional amount of methyl iodide (1.6 equivalents) and an additional amount of the same base (1.0 equivalents).

Scheme 5 Table

Bromoquinolines



XX

R^1	R^2	R^3	Bromoquinoline (XX)
SO_2Me	H	H	Q1
SO_2Me	Me	H	Q2
SO_2Me	Me	Me	Q3
CN	H	H	Q4
CN	Me	Me	Q5

Bromoquinoline **Q1**

6-(methylsulfonyl)methyl- 8-bromoquinoline

Bromoquinoline **Q1** was prepared by the following procedure. DMF (500mL) was added to 6-bromomethyl-8-bromoquinoline (60g, 200mmol) (described in International Patent Publication WO 94/22852) and sodium methanesulfinate

(27.6g, 270mmol). After stirring overnight at r.t., the mixture was quenched with H_2O (2000mL), stirred for one hour, isolated by filtration and washed with Et_2O to yield 6-(methylsulfonyl)methyl-8-bromoquinoline.

Bromoquinoline **Q2**

6-[1-(methylsulfonyl)ethyl]-8-bromoquinoline

Bromoquinoline **Q2** was prepared by the following procedure. To a solution of bromoquinoline **Q1** (16.1g, 54mmol) in THF (500mL) at –78°C, was added potassium *t*-butoxide (59mL, 1N in THF). After 0.5h at –78°C, the resulting mixture was stirred at 0°C for 45min and then transferred by canula dropwise into a solution of MeI (16.7mL , 268.3mmol) in THF (160mL). After stirring overnight at r.t., the mixture was neutralised with saturated NH_4Cl solution and extracted with EtOAc. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Stirring in ether, followed by isolation by filtration gave 6-[1-(methylsulfonyl)ethyl]-8-bromoquinoline.

Bromoquinoline **Q3**

6-[1-methyl-1-(methylsulfonyl)ethyl]-8-bromoquinoline

Bromoquinoline **Q3** was prepared by the following procedure. To a solution of bromoquinoline **Q2** (15.7g, 50mmol) in THF (500mL) at –78°C, was added potassium *t*-butoxide (55mL, 1N in THF). After stirring 0.5h at –78°C, the resulting mixture was stirred at 0°C for 45min and then transfered dropwise into a solution of MeI (15.6mL, 250mmol) in THF (40mL) at 0°C. After stirring overnight at r.t., the mixture was neutralised with saturated NH_4Cl solution, and extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Stirring in ether, followed by isolation by filtration gave 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-bromoquinoline.

Bromoquinoline **Q4**

6-cyanomethyl-8-bromoquinoline

Bromoquinoline **Q4** was prepared by the following procedure. DMF (10mL) and H_2O (5mL) were added to 6-bromomethyl-8-bromoquinoline (3g, 10mmol) (described in International Patent Publication WO 94/22852) and potassium cyanide (1.6g, 25mmol). After heating at 100°C for 1 hour, the resulting mixture was quenched with H_2O (100mL) and extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 3:1) yielded 6-cyanomethyl-8-bromoquinoline.

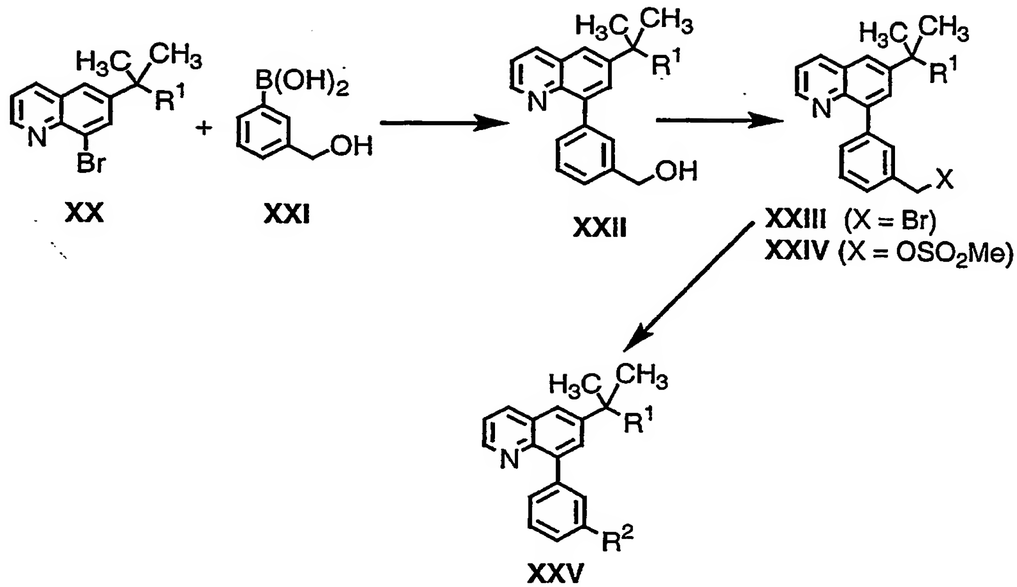
Bromoquinoline **Q5**
6-[1-methyl-1-cyanoethyl]-8-bromoquinoline

Bromoquinoline **Q5** was prepared by the following procedure. To a solution of bromoquinoline **Q4** (3g, 12.1mmol) in THF (100mL) at –78°C, was added MeI (1.7mL, 27mmol) followed by potassium *t*-butoxide (27mL, 27mmol). After 2h at –78°C, the mixture was warmed to 0°C and was neutralised with saturated NH_4Cl solution then extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 3:1) yielded 6-[1-methyl-1-cyanoethyl]-8-bromoquinoline.

The Benzyl Phosphorus Reagents utilized to prepare the compounds of this invention can be made according to Scheme 6 shown below:

SCHEME 6

Preparation of Benzyl Phosphorus Reagents



R^1	R^2	Benz. Phos. Reag.(XXV)
H	$CH_2P(Ph)_3^+Br^-$	P1
H	$CH_2P(O)(OEt)_2$	P2
CN	$CH_2P(O)(OEt)_2$	P3

The arylquinolines of the formula **XXII** may be prepared by coupling bromoquinoline **XX** with the boronic acid **XXI** by heating in the presence of a catalyst such as $Pd(PPh_3)_4$ and a base such as sodium carbonate (aqueous) in a solvent such as a DME. The alcohol **XXII** may be converted to the bromide **XXIII** by treatment with HBr (aq) in a solvent such as acetic acid. The alcohol **XXII** may be converted to the methyl sulfonate ester **XXIV** by methanesulfonyl chloride in the presence of a base such as triethylamine in a solvent such as dichloromethane. The benzyl phosphorous reagents **XXV** may be prepared either by heating **XXIII** in the presence of PPh_3 in a solvent such as acetonitrile or by treating **XXIII** or **XXIV** with diethylphosphite and a base such as potassium *t*-butoxide in a solvent such as THF.

Benzylphosphonium Bromide **P1**

[3-(6-Isopropyl-8-quinolinyl)benzyl](triphenyl)phosphonium Bromide

Benzylphosphonium Bromide **P1** was prepared by the following procedure.

Step 1: 6-Isopropyl-8-[3-(hydroxymethyl)phenyl]quinoline

A mixture of 6-isopropyl-8-Bromoquinoline (11.1g, 44.4mmol) (described in International Patent Publication WO 94/22852), 3-(hydroxymethyl)phenylboronic acid (8.70g, 57.2mmol), Na_2CO_3 (2M, 71mL, 142mmol) and $Pd(PPh_3)_4$ (2.51mg, 2.17mmol) in 280mL of DME was stirred at 80°C for 5h. The resulting mixture was cooled to r.t., diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (Hex/EtOAc, 1/1) and stirring in CH_2Cl_2/hexane (1/9) yielded 6-Isopropyl-8-[3-(hydroxymethyl)phenyl]quinoline as a white solid.

Step 2: 6-Isopropyl-8-[3-(bromomethyl)phenyl]quinoline

A suspension of the hydroxymethyl product compound from present step 1 (7.40g, 26.7mmol) in AcOH (50mL) and HBr (50mL, 48% aq) was stirred for 12h at 100°C. The mixture was cooled to r.t., poured into NaOH (2N) in ice, the pH was adjusted to 8 and the mixture was diluted with ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield 6-Isopropyl-8-[3-(bromomethyl)phenyl]quinoline as a yellow solid.

Step 3: [3-(6-Isopropyl-8-quinolinyl)benzyl](triphenyl)phosphonium Bromide

To a solution of the bromomethyl product compound from present step 2 (3.807g, 11.1mmol) in 40mL of CH_3CN was added triphenylphosphine (3.22g, 12.3mmol). The mixture was stirred at 60°C for 12h, cooled to r.t., diluted with ether, filtered, and washed with ether to yield [3-(6-Isopropyl-8-quinolinyl)benzyl](triphenyl)phosphonium Bromide.

Benzylphosphonate **P2**

Diethyl 3-(6-isopropyl-8-quinolinyl)benzylphosphonate

Benzylphosphonate **P2** was prepared by the following procedure. The bromomethyl compound from from step 2 above of the synthesis of **P1** (11.34g, 1eq) was dissolved in THF (170mL). Diethylphosphite (3.87mL, 1.05eq) was added and the solution was cooled down to 0°C. Next, *t*-BuOK (3.87mL, 1N in THF) was added slowly. The reaction was stirred 2h and the quenched by addition of NH_4Cl(sat), water and EtOAc. The organic phase was separated and washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel (hexane:EtOAc, 1/9) gave Diethyl 3-(6-isopropyl-8-quinolinyl)benzylphosphonate as a clear oil.

Benzylphosphonate **P3**

Diethyl 3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]benzylphosphonate

Benzylphosphonate **P3** was prepared by the following procedure.

Step 1: 6-(1-Cyano-1-methylethyl)-8-[3-(hydroxymethyl)phenyl]quinoline

Following step 1 described above of the procedure for Benzylphosphonium Bromide **P1**, but substituting the bromoquinoline **Q5** for 6-isopropyl-8-bromoquinoline as the starting material, 6-(1-Cyano-1-methylethyl)-8-[3-(hydroxymethyl)phenyl]quinoline was obtained.

Step 2: 3-[6-(1-Cyano-1-methylethyl)-8-quinolinyl]benzyl methanesulfonate

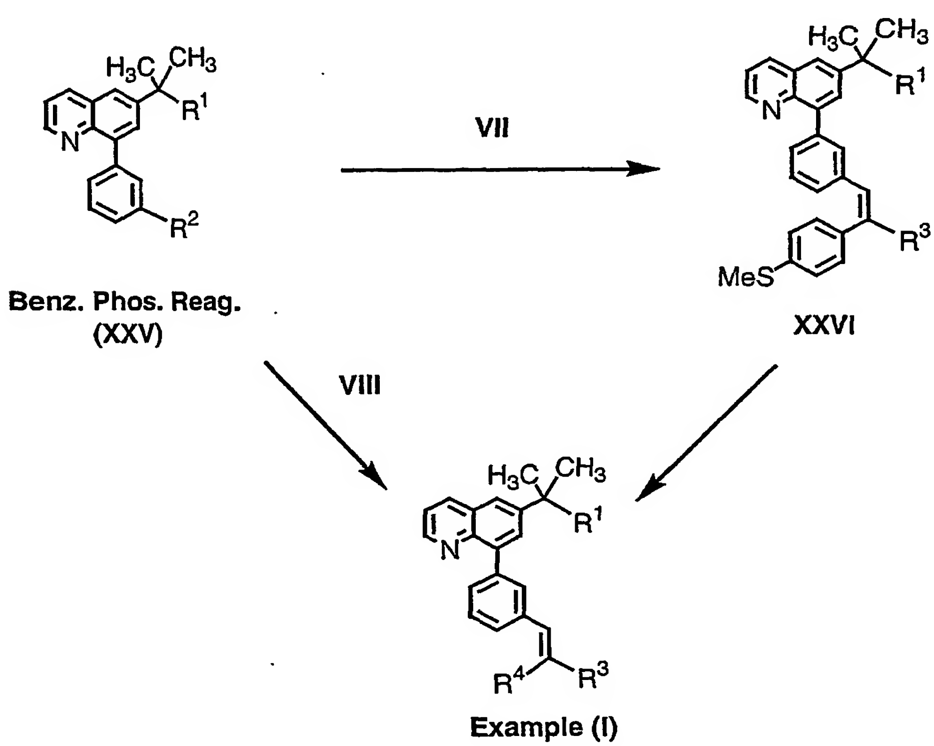
To a solution of the alcohol 6-(1-Cyano-1-methylethyl)-8-[3-(hydroxymethyl)phenyl]quinoline from present step 1 (5.15g, 17mmol) in CH_2Cl_2 (150mL) at –78°C was added Et_3N (3.6mL, 26mmol) and methanesulfonyl chloride ("MsCl") (1.6mL, 21mmol). After 0.5h at –78°C, the mixture was neutralised with saturated NH_4Cl solution, diluted with water and extracted with ether. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated to yield 3-[6-(1-Cyano-1-methylethyl)-8-quinolinyl]benzyl methanesulfonate as a white foam.

Step 3: Diethyl 3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]benzylphosphonate

To a solution of diethylphosphite (2.5mL, 18mmol) in THF (100mL) at –78°C was added potassium *t*-butoxide (1M, THF, 16mL, 16mmol) and the mesylate compound 3-[6-(1-Cyano-1-methylethyl)-8-quinolinyl]benzyl methanesulfonate from present step 2 (5.1g, 13.5mmol). After 0.5h at –78°C and 12h at r.t., the resulting mixture was neutralised with saturated NH_4Cl solution, diluted with water and extracted with ether. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 1:4 to 1:10) yielded Diethyl 3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]benzylphosphonate as an oil.

SCHEME 7

Benzyphosphorous Reagent – Ketone Coupling



Compounds corresponding to the formula **I** may be prepared using the reaction pathways outlined in Scheme 7 above. The compound **XXVI** may be

obtained by adding a solution of the ketone **VII** in a solvent such as THF to a mixture of the benzylphosphorous reagent **XXV** and a base such as potassium *t*-butoxide in a solvent such as THF. The compounds corresponding to the formula **I** may then be prepared by treating **XXVI** with oxone in a mixture of solvents such as THF/MeOH/water. Alternatively the compounds of formula **I** may be prepared by reacting the ketone **VIII** with **XXV** in the presence of a base such as potassium *t*-butoxide in a solvent such as THF.

Referring to Scheme 7 above and Table 1 below, the coupling of the ketones with the benzyl phosphorous reagents resulted in the tabulated Examples.

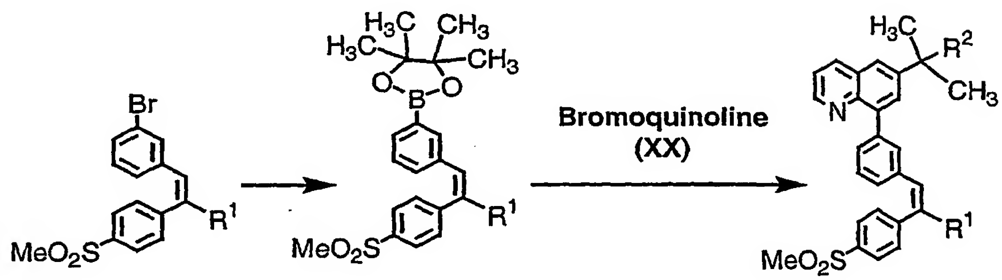
Table1

Benz. Phos. Reag.	Ketone	Example
P2	K3	1
P2	K3	2
P1	K5	3
P1	K2	4
P2	K1	5
P2	K1	6
P2	K6	7
P3	K6	8
P3	K2	9
P2	Commercial	30
P2	K7	31
P2	K7	32
P2	K8	33
P2	K8	34
P2	K9	35
P3	K8	36
P3	K8	37

Table1		
Benz. Phos. Reag.	Ketone	Example
P3	K9	38
P3	K10	39

SCHEME 8

Aryl Bromide – Bromoquinoline Coupling



Aryl Bromide (XVIII) **Boronate (used in situ)** **Example (I)**

Referring to Scheme 8, compounds corresponding to the formula **I** may be prepared by *in situ* conversion of the aryl bromide **XVIII** to the corresponding boronate ester by heating with diboron pinacol ester, a catalyst such as [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) and a base such as potassium acetate in a solvent such as DMF, followed by the addition of the bromoquinoline **XX**, an additional amount of the same catalyst, an additional amount of a base such as sodium carbonate (aqueous) and an additional period of heating.

Referring to Scheme 8 above, Table 2 and Table 2 appendix below, the coupling of the Aryl Bromide with the Bromoquinoline resulted in the tabulated Examples.

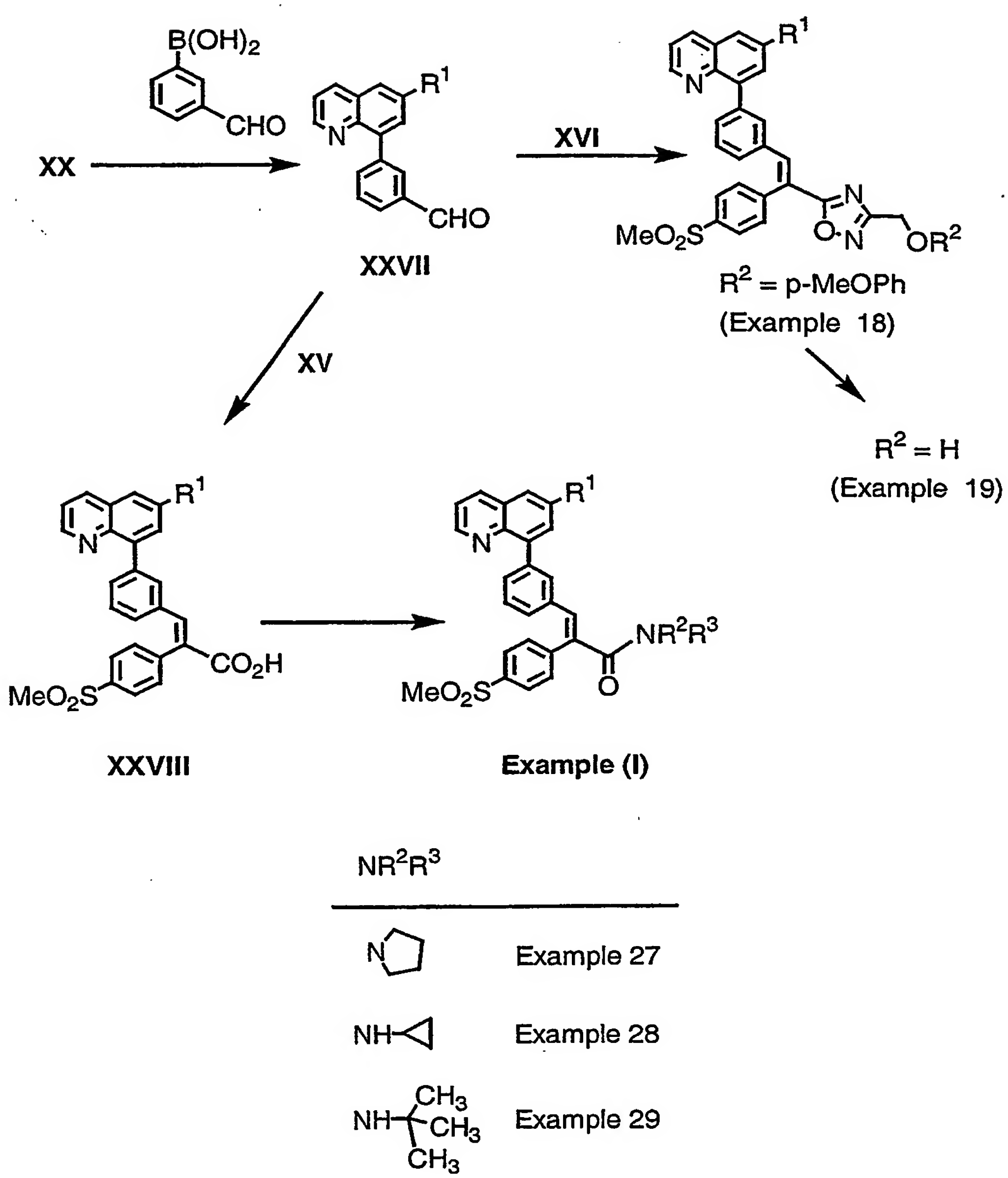
Table 2		
Aryl Bromide	**Bromoquinoline**	**Example**
AB5	Q3	14
AB5	Q3	15
AB2	Q5	16
AB2	Q5	17
AB2	Q3	20
AB1	Q5	21
AB5	Q5	22
AB3	Q5	23
AB4	Q5	24
AB1	WO 94/22852	25
AB5	WO 94/22852	26

Table 2 appendix

Aryl Bromide	Bromoquinoline	Example
AB6	Q5	43

Compounds of this invention can be prepared by following Scheme 9 shown below.

SCHEME 9



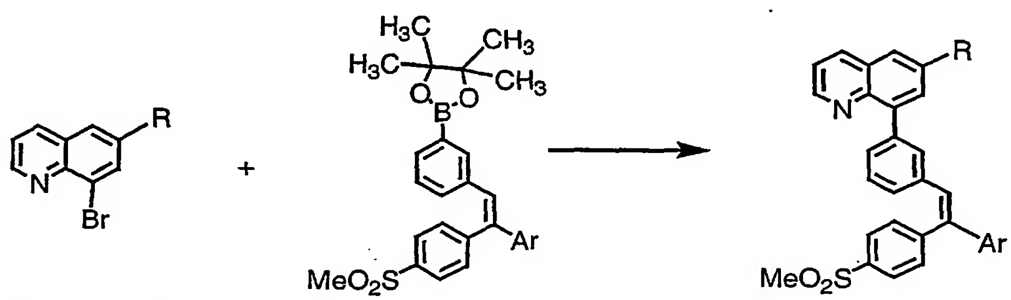
Scheme 9 outlines the preparation of compounds of formula I where the aldehyde **XXVII** may be prepared by heating the bromoquinoline **XX**, 3-formylbenzeneboronic acid, a catalyst such as $Pd(PPh_3)_4$ and a base such as sodium

carbonate (aqueous) in a solvent such as DME. The aldehyde **XXVII** may be converted to Example 18 by heating with **XVI** in the presence of a base such as piperidine in a solvent such as toluene. Example 19 may be obtained by treatment of Example 18 with cerric ammonium nitrate ("CAN") in a mixture of solvents such as acetonitrile/water. Alternatively the aldehyde **XXVII** may be converted to the unsaturated acid **XXVIII** by heating with **XV** and a base such as piperidine in a solvent such as toluene. The acid **XXVIII** may then be converted to the amide **I** (Example 27, 28 and 29) by treatment with a coupling system such as EDCI, HOBt, and an amine in a solvent such as DMF.

Compounds of this invention can be prepared by coupling Bromoquinoline compounds with Boronate compounds according to Scheme 10 below.

SCHEME 10

Bromoquinoline—Boronate Coupling



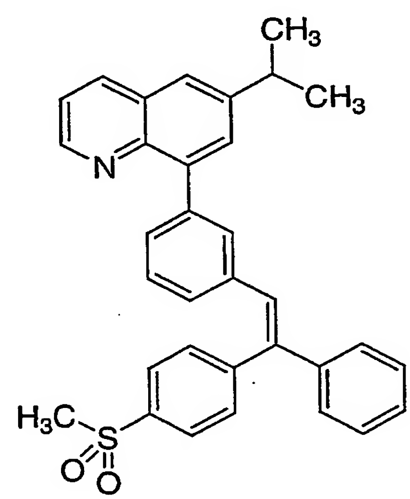
Bromoquinoline (XX) **Boronate (XII)** **Example (I)**

Scheme 10 describes how compounds of formula I may be obtained by coupling the bromoquinoline **XX** with the boronate ester **XII** in the presence of a catalyst such as $Pd(OAc)_2$, PPh_3, and a base such as sodium carbonate (aqueous) in a solvent such as *n*-propanol. Referring to Table 3, the coupling of the Bromoquinoline with Boronate resulted in the tabulated Examples.

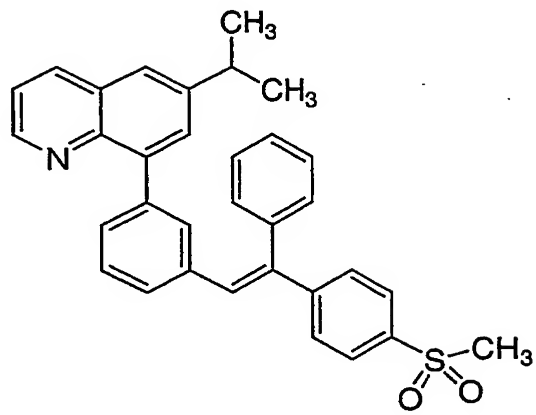
Table 3		
Bromoquinoline	**Boronate**	**Example**
Q2	B2	10
Q3	B2	11
Q2	B1	12
Q3	B1	13
Q3	B3	40
Q3	B3	41
Q3	B4	42

EXAMPLES 1 and 2

6-isopropyl-8-(3-{(Z/E)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl}phenyl)quinoline



Example 1



Example 2

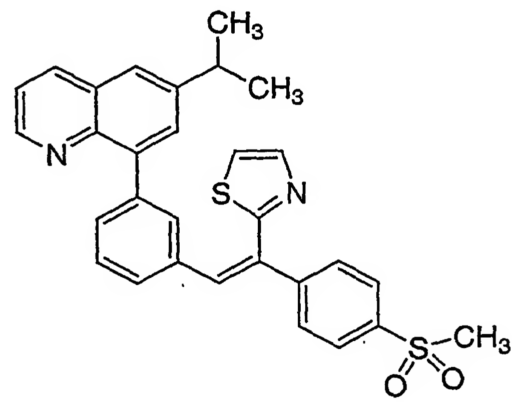
Examples 1 and 2 were prepared by the following procedure. To a mixture of benzylphosphonate **P2** (330mg, 0.83mmol) and ketone **K3** (200mg, 0.77mmol) in THF (6mL) at r.t. was added potassium *t*-butoxide (1M, THF, 0.83mL, 0.83mmol). After 1h at r.t., the mixture was diluted with water and extracted with Et_2O. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 7:3) produced Examples 1 and 2 as white foams with one product being less polar than the other product. Example 1 was the less polar Z-isomer and Example 2 was the more polar E-isomer.

Example 1: NMR ^{1}H (400MHz, Acetone-d_6) ∂ 8.79 (q, 1H), 8.28 (q, 1H), 7.94 (d, 2H), 7.73 (d, 1H), 7.6-7.1 (m, 14H), 3.14 (m, 1H), 2.97 (s, 3H), 1.34 (d, 6H).

Example 2: NMR ^{1}H (400MHz, Acetone-d_6) ∂ 8.78 (q, 1H), 8.25 (q, 1H), 7.89 (d, 2H), 7.71 (d, 1H), 7.6 (m, 3H), 7.45 (m, 3H), 7.39-7.2 (m, 8H), 3.11 (m, 4H), 1.34 (d, 6H).

EXAMPLE 3

6-isopropyl-8-{3-[(E/Z)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline



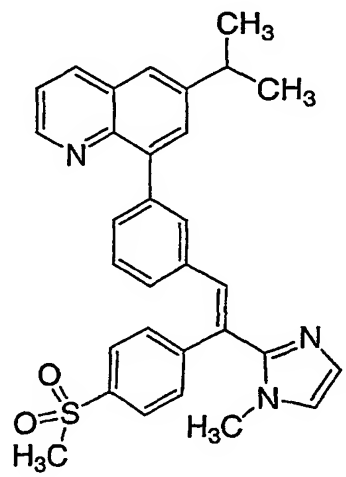
Example 3 was prepared by the following procedure. To a suspension of the benzylphosphonium bromide **P1** (320mg, 0.531mmol) in 2.5mL THF at -78°C was added *t*-BuOK (1.0M in THF, 0.55mL, 0.55mmol) dropwise and the resulting red solution was stirred 30min at 0°C . To this ylide at –78°C was then added ketone **K5** (122mg, 0.455mmol) in 2mL of THF dropwise. The mixture was warmed to r.t., then stirred for 1h, quenched with a NH_4Cl (sat.) and diluted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (Silica cartridge, Hex/EtOAc 10 to 100% in 20min) yielded Example 3 (1.5 to 1 mixture of isomers).

NMR ^1H (500MHz in acetone-d_6) ∂ 8.79-8.78 (m, 1H), 8.26-8.23 (m, 1H), 8.01-7.92 (m, 3H), 7.84 (d, 0.4H, minor), 7.78 (d, 0.6H, major), 7.73-7.47 (m, 10H), 7.43 (dd, 1H), 7.34 (t, 0.6H, major), 7.27 (t, 0.4H, minor), 7.18 (d, 0.6H, major), 7.09 (d, 0.4H, minor), 3.12 (m, 1H), 3.11 (s, 1.8H, major), 2.99 (s, 1.2H, minor), 1.36-1.33 (m, 6H).

MS (M+1) 511.

EXAMPLE 4

6-isopropyl-8-(3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline



Example 4 was prepared by the following procedure.

Step 1: 6-isopropyl-8-(3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylthio)phenyl]ethenyl}phenyl)quinoline

Following the procedure for Example 3 but substituting the ketone **K2** for **K5** as the starting material, 6-isopropyl-8-(3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylthio)phenyl]ethenyl}phenyl)quinoline was obtained.

Step 2: 6-isopropyl-8-(3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline

Following the procedure used for the preparation of the boronate **B1** (step 2 of Scheme 2) but substituting the sulfide obtained in the present step 1 for

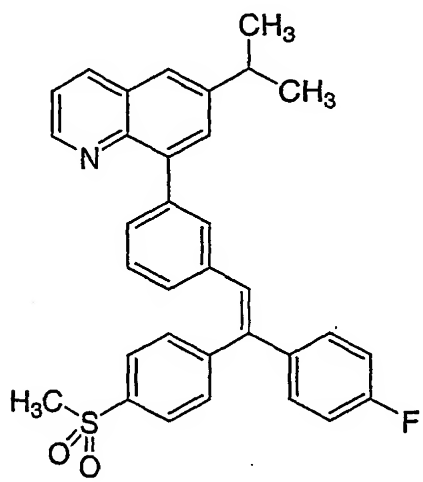
(E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene as the starting material, Example 4 was obtained.

NMR ^{1}H (500 MHz in acetone-d_6) ∂ 8.77 (dd, 1H), 8.24 (dd, 1H), 7.88 (d, 2H), 7.71(d, 1H), 7.59 (d, 1H), 7.53 (d, 2H), 7.48 (d, 2H), 7.41 (dd, 1H), 7.28 (t, 1H), 7.23 (s, 1H), 7.15 (d, 1H), 7.07 (d, 1H), 6.95 (d, 1H), 3.51 (s, 3H), 3.10 (m, 1H), 2.99 (s, 3H), 1.32 (d, 6H).

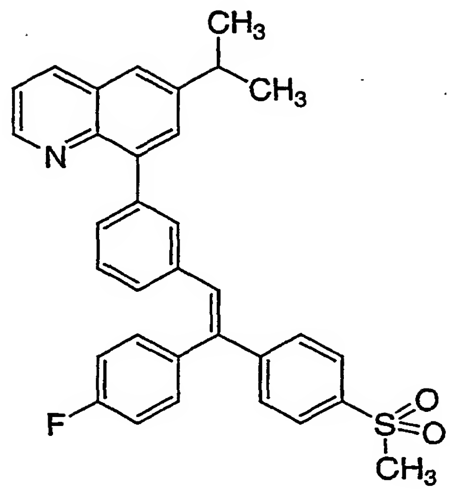
MS: (m+2): 509.4

EXAMPLES 5 and 6

6-isopropyl-8-(3-{(Z/E)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline



Example 5



Example 6

Examples 5 and 6 were prepared by the following procedure.

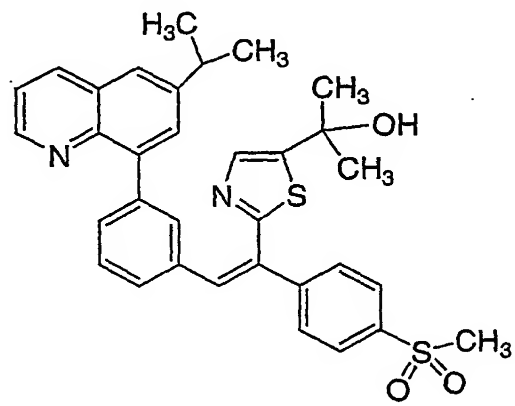
Following the procedure for Example 1 but substituting the ketone **K1** for **K3** as the starting material, and purification by flash chromatography (50%EtOAc/50%Hexanes) yielded Examples 5 and 6.

NMR ^{1}H (500MHz in acetone-d_6) Example 5: Major (Z) isomer: ∂ 8.78 (dd, 1H), 8.25 (dd, 1H), 7.93 (d, 2H), 7.72 (d, 1H), 7.55-7.40 (m, 6H), 7.35 (m, 2H), 7.25 (t, 1H), 7.23 (s, 1H), 7.11 (t, 2H), 7.05 (d, 1H), 3.12 (m, 1H), 2.96 (s, 3H), 1.34 (d, 6H).

NMR ^{1}H (500MHz in acetone-d_6) Example 6: Minor (E) isomer: ∂ 8.78 (dd, 1H), 8.35 (dd, 1H), 7.93 (d, 2H), 7.72 (d, 1H), 7.65-7.55 (m, 3H), 7.45 (dd, 1H), 7.35-7.15 (m, 9H), 3.12 (m, 4H), 1.34 (d, 6H).

EXAMPLE 7

2-(2-{(E/Z)-2-[3-(6-isopropyl-8-quinolinyl)phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl}-1,3-thiazol-5-yl)-2-propanol



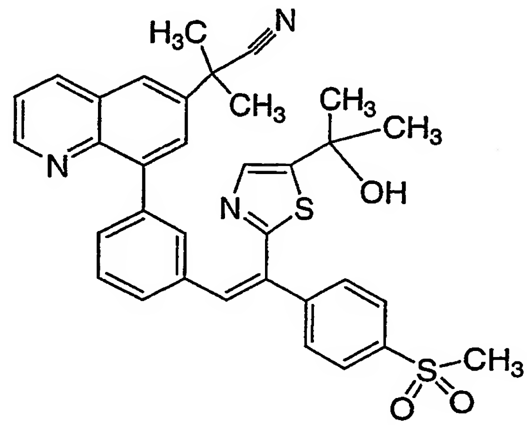
Example 7 was prepared by following the procedure for Example 1 but substituting the ketone **K6** for **K3** as the starting material. Purification by flash chromatography (100%EtOAc) yielded Example 7 as a mixture of isomers.

NMR ^{1}H (400MHz in acetone-d_6) ∂ 8.80 (m, 1H), 8.30 (m, 1H), 8.05 (d(major), 1.44H), 7.93 (d(minor), 0.55H), 7.85 (s(major), 0.72H), 7.77 (s,(minor), 0.28H), 7.75-7.45 (m, 7H) 7.35 (t(minor), 0.28H), 7.28 (t,(major), 0.72H), 7.21 (d(minor), 0.28H), 7.10 (d(major), 0.72H), 4.7 (m, 1H), 3.15 (m, 1H), 3.15 (s(minor), 0.84), 2.99 (s(major), 2.16H), 1.60 (m, 6H), 1.35 (m, 6H).

MS (m+1): 569.6

EXAMPLE 8

2-[8-(3-{(E/Z)-2-[5-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]-2-methylpropanenitrile



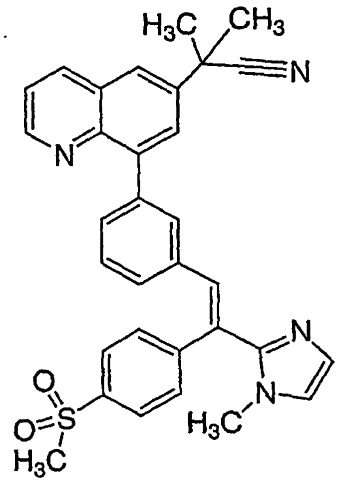
Example 8 was prepared by following the procedure for Example 1 but substituting the ketone **K6** for **K3** and the benzyl phosponate **P3** for **P2** as the starting materials. Purification by flash chromatography (20%CH_2Cl_2/80%EtOAc) yielded Example 8 as a mixture of isomers.

NMR ^{1}H (400MHz in acetone-d_6) ∂ 8.92 (m, 1H), 8.45 (m, 1H), 8.10 (m, 1H), 8.05 (m, 1H), 7.93 (m, 1H), 7.85 (m, 2H), 7.77-7.55 (m, XH), 7.40 (t(minor), 0.43H), 7.28 (t,(major), 0.57H), 7.21 (d(minor), 0.43H), 7.10(d(major), 0.57H), 4.67 (s,(major), 0.57H), 4.63 (s(minor), 0.43H), 3.15 (s(minor), 1.3H), 2.99 (s(major), 1.7H), 1.90 (m, 6H), 1.65 (s,(major), 3.4H), 1.45 (s(minor), 2.6H).

MS (m+1): 594.6

EXAMPLE 9

2-methyl-2-[8-(3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]propanenitrile



Example 9 was prepared by the following procedure.

Step 1: 2-methyl-2-[8-(3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylthio)phenyl]ethenyl}phenyl)-6-quinolinyl]propanenitrile was prepared by following the procedure for Example 1 but substituting the ketone **K2** for **K3** and the benzyl phosphonate **P3** for **P2** as the starting materials.

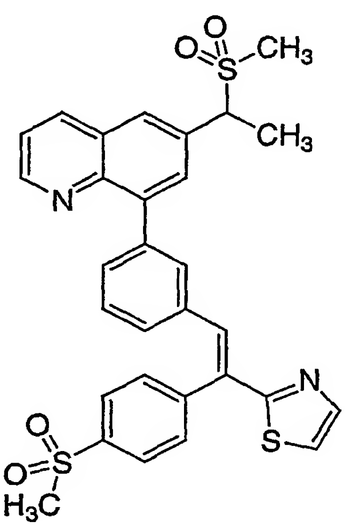
Step 2: 2-methyl-2-[8-(3-{(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]propanenitrile, Example 9, was prepared by following the procedure used for the preparation of the boronate **B1** (step 2 of Scheme 2) but substituting the sulfide obtained in present step 1 for (E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene as the starting material. Example 9 was obtained after purification by flash chromatography (97%EtOAc/3%Et_3N).

NMR [1]H (400MHz in acetone-d_6) ∂ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.10 (d, 1H), 7.93 (d, 2H), 7.76 (d, 1H), 7.60-7.50 (m, 5H), 7.38 (t, 1H), 7.35 (s, 1H), 7.19 (m, 1H), 7.10 (m, 1H), 6.95 (m, 1H), 3.55 (s, 3H), 3.00 (s, 3H), 1.85 (s, 6H).

MS (m+1): 533.3

EXAMPLE 10

6-[1-(methylsulfonyl)ethyl]-8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline



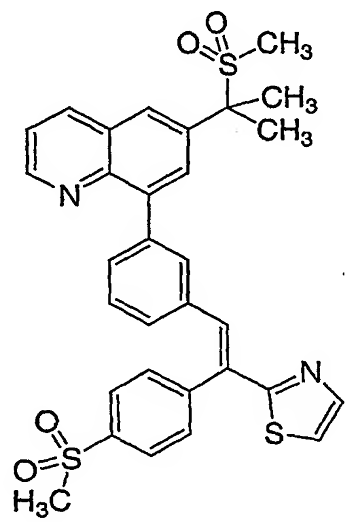
Example 10 was prepared by the following procedure. A mixture of bromoquinoline **Q2** (105mg, 0.33mmol), boronate **B2** (236mg, 0.51mmol), Na_2CO_3 (2M, 0.65mL, 1.3mmol), $Pd(OAc)_2$ (6.3mg, 0.028mmol) and PPh_3 (28mg, 0.11mmol) in 4mL of *n*-propanol was stirred at 90°C for 2h. The mixture was cooled to r.t., diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (Tol/Acetone; 4/1) and stirring in Hexane/EtOAc yielded Example 10 (single isomer) as a white solid.

NMR ^1H (400MHz, Acetone-d_6) ∂ 8.89 (dd, 1H), 8.39 (dd, 1H), 8.07 (d, 1H), 8.03 (d, 2H), 7.94 (s, 1H), 7.86 (d, 1H), 7.71-7.68 (m, 3H) 7.62-7.60 (m, 2H), 7.55 (dd, 1H), 7.45 (s, 1H) 7.34 (t, 1H), 7.18 (d, 1H), 4.67 (q, 1H), 3.04 (s, 3H), 2.86 (s, 3H) 1.88 (s,3H)

MS (M + 1) 576.

EXAMPLE 11

6-[1-methyl-1-(methylsulfonyl)ethyl]-8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline



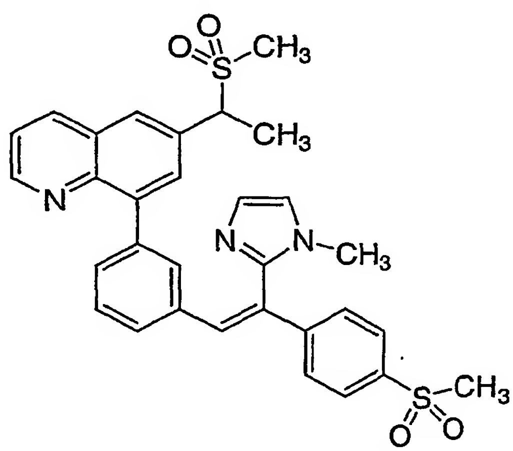
Example 11 was prepared by following the procedure described in Example 10 but substituting bromoquinoline **Q3** for **Q2** and using boronate **B2**. Flash chromatography (Tol/Acetone; 9/1) and stirring in EtOAc/Hex yielded Example 11 (single isomer) as a white solid.

NMR ^1H (400MHz, Acetone-d_6): ∂ 8.90 (dd, 1H), 8.41 (dd, 1H), 8.23 (s, 1H), 8.02-7.99 (d, 3H), 7.95 (s, 1H), 7.86 (d, 1H), 7.70 (d, 2H), 7.60-7.54 (m, 4H), 7.32 (t, 1H), 7.13 (d, 1H), 3.00 (s, 3H), 2.69 (s, 3H), 1.96 (s, 6H)

MS (M+1) 523.

EXAMPLE 12

8-(3-{(Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-(methylsulfonyl)ethyl]quinoline



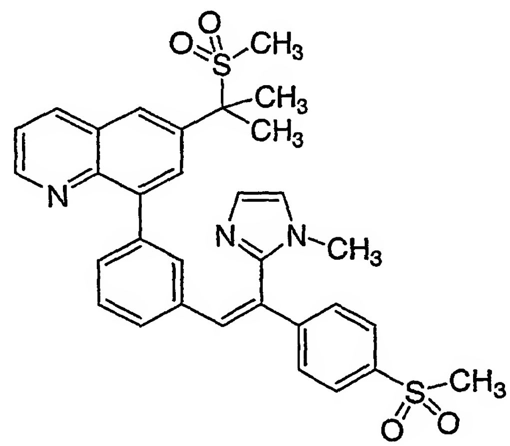
Example 12 was prepared following the procedure described in Example 10 using the bromoquinoline **Q2** but substituting the boronate **B1** for boronate **B2**. Flash chromatography (95%CH_2Cl_2/5%EtOH) yielded the Example 12 compound.

NMR ^1H (400MHz in acetone-d_6) ∂ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.10 (s, 1H), 7.93 (d, 2H), 7.76-7.65 (m, 4H), 7.59 (dd, 1H), 7.39 (t, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 7.05 (m, 2H), 4.70 (q, 1H), 3.40 (s, 3H), 3.13 (s, 3H), 2.93 (s, 3H), 1.87 (d, 3H).

MS (m+1): 572.4

EXAMPLE 13

8-(3-{(Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline



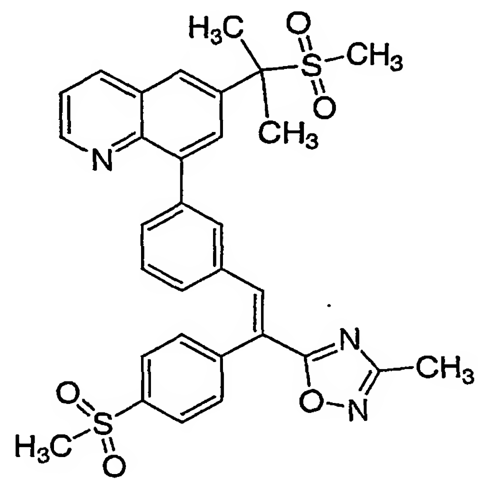
Example 13 was prepared following the procedure described in Example 10 but substituting the bromoquinoline **Q3** for **Q2** and substituting the boronate **B1** for boronate **B2**. Flash chromatography (95%EtOAc/5% Et_3N) produced Example 13 (single isomer) as a foam.

NMR ^{1}H (400MHz in acetone-d_6) ∂ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.37 (d, 1H), 8.05 (d, 1H), 7.93 (d, 2H), 7.76 (d, 1H), 7.69 (d, 2H), 7.65 (d, 1H), 7.59 (dd, 1H), 7.38 (t, 1H), 7.31 (s, 1H), 7.18 (s, 1H), 7.05 (m, 2H), 3.40 (s, 3H), 3.13 (s, 3H), 2.70 (s, 3H), 1.95 (s, 6H).

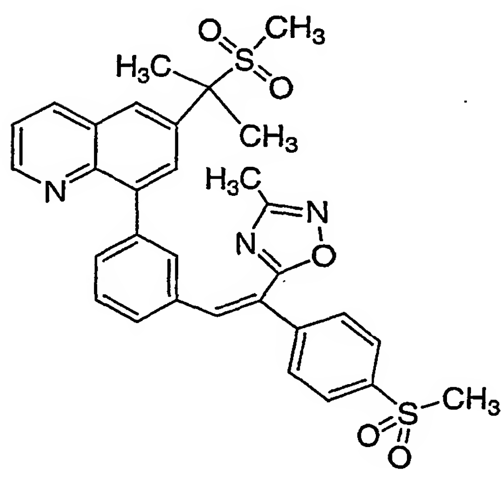
MS (m+1): 586.2

EXAMPLES 14 and 15

6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-{(E/Z)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline



Example 14



Example 15

Examples 14 and 15 were prepared by the following procedure. A solution of the aryl bromide **AB5** (249mg, 0.57mmol), diboron pinacol ester (167mg, 0.66mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (12mg, 0.015mmol) and potassium acetate (176mg, 1.8mmol) in DMF (*N,N*-Dimethylformamide) (10mL) was degassed and stirred at 80°C for 3h. To that resulting mixture at 25°C was then added the bromoquinoline **Q3** (150mg, 0.46mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (12mg, 0.015mmol) and sodium carbonate (0.6mL, 2M). After degassing, the mixture was heated at 80°C overnight. The mixture was then cooled to r.t. quenched with H_2O, and extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (hexane:EtOAc:Et_3N, 22:68:10 then hexane:EtOAc, 3:1) yielded both isomers (Example 14 and Example 15).

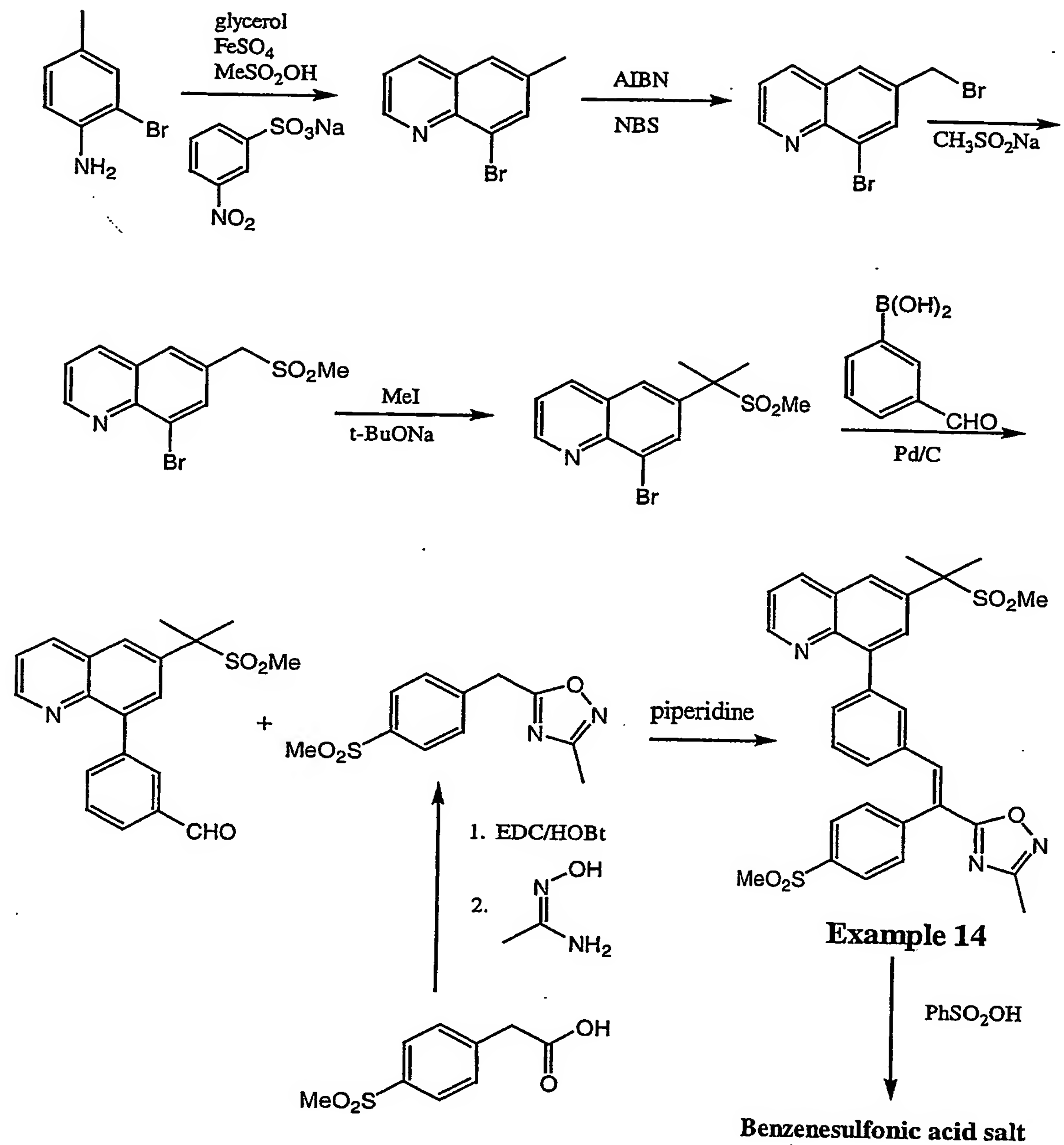
NMR ^1H (500MHz, Acetone-d_6) Major(E) isomer (Example 14): ∂ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.25 (d, 1H), 8.12 (s, 1H), 8.02 (d, 1H), 8.00 (d, 2H), 7.70 (m, 3H), 7.64 (s, 1H), 7.55 (dd, 1H), 7.38 (t, 1H), 7.23 (d, 1H), 3.03 (s, 3H), 2.69 (s, 3H), 2.33 (s, 3H), 1.96 (s, 6H).

MS (M+1): 588.2

Minor(Z) isomer (Example 15): ∂ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.29 (d, 1H), 8.07 (d, 1H), 7.99 (d, 2H), 7.88 (s, 1H), 7.75 (m, 3H), 7.62 (s, 1H), 7.58 (q, 1H), 7.48 (t, 1H), 7.24 (d, 1H) 3.16 (s, 3H), 2.70 (s, 3H), 2.38 (s, 3H), 2.00 (s, 6H).

MS (M+1): 588.2

Alternatively, **Example 14** can be made by the following procedure:



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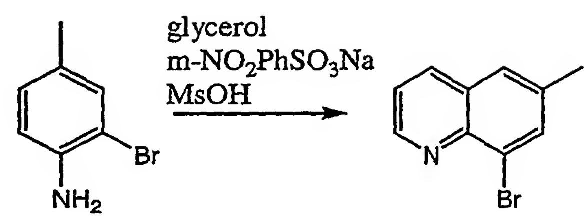
Br
NH2
N
Br
AIBN
NBS
Br
CH3SO2Na
SO2Me
MeI
t-BuONa
B(OH)2
CHO
Pd/C
CHO
+
MeO2S
O
N
piperidine
1. EDC/HOBt
2.
OH
NH2
OH
O
Example 14
PhSO2OH
Benzenesulfonic acid salt

Step 1. Skraup Reaction

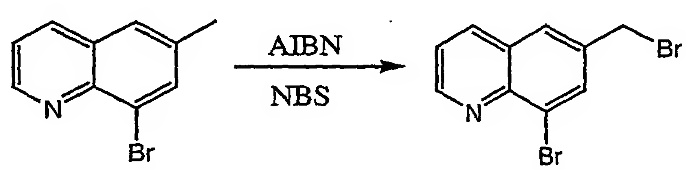


To methanesulfonic acid (8-10 equiv) at 20°C was added sodium m-nitrobenzenesulfonate (0.6-0.8 equiv), followed by iron sulfate heptahydrate (0.01-0.05 equiv). To the resulting mixture was added 2-bromo-4-methylaniline (1 equiv).

Glycerol (2-3 equiv) was added and the resulting solution was heated at 120-140°C and aged until the reaction was complete.

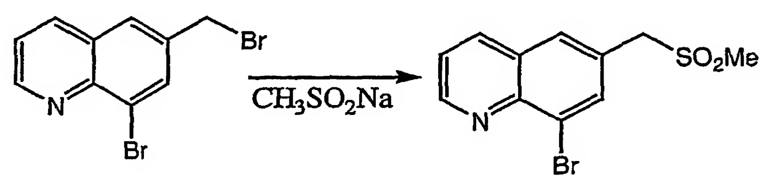
The mixture was cooled to 70-90°C and diluted with water. The solution was then cooled to about 20°C, and neutralized with aqueous NaOH and sodium bicarbonate. MTBE (methyl t-butyl ether) was added and the mixture was filtered and the phases were separated (the product was in the MTBE layer).

Step 2. Bromination



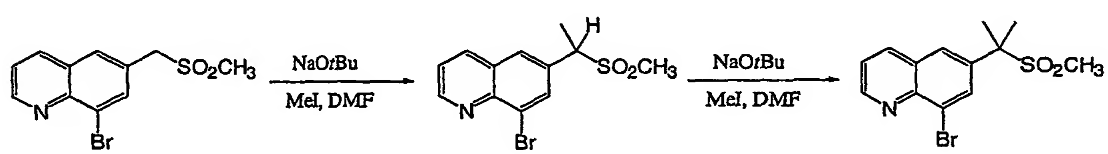
The MTBE solution from step 1 was solvent switched to chlorobenzene. After filtered through Silica gel and partially concentrated, N-bromosuccinimide (NBS, 0.6-0.8 equiv) and 2,2'-azobisisobutylnitrile (AIBN, 0.01-0.1 equiv) were added. The degassed mixture was heated at 55-85°C. The resulting mixture was diluted with cyclohexane. Additional NBS (0.3-0.5 equiv) and AIBN (0.01-0.05 equiv) were added. The degassed mixture was heated at about 55-85°C until reaction completed. The mixture was cooled at 10-40°C and diluted with cyclohexane and aged. The solid was isolated by filtration.

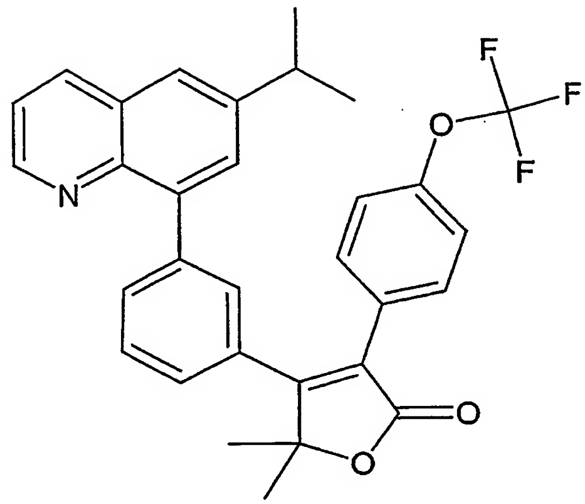
Step 3. Sulfone Formation



To a solution of bromomethyl-bromoquinoline (product from previous step, 1 equiv) in DMF was added powdered sodium methanesulfinate (1.0-1.5 equiv) at 10-60 °C. The mixture was heated at about 50-70°C for 30min. The mixture was diluted with water while maintaining temp at about 50-70 °C with vigorous stirring, then cooled to about 10-20°C and aged. The mixture was filtered and the solid washed sequentially with 1:4 DMF/water and then water and dried.

Step 4. Methylation

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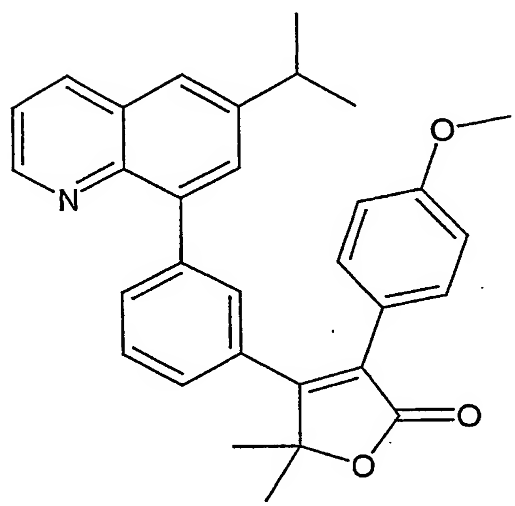
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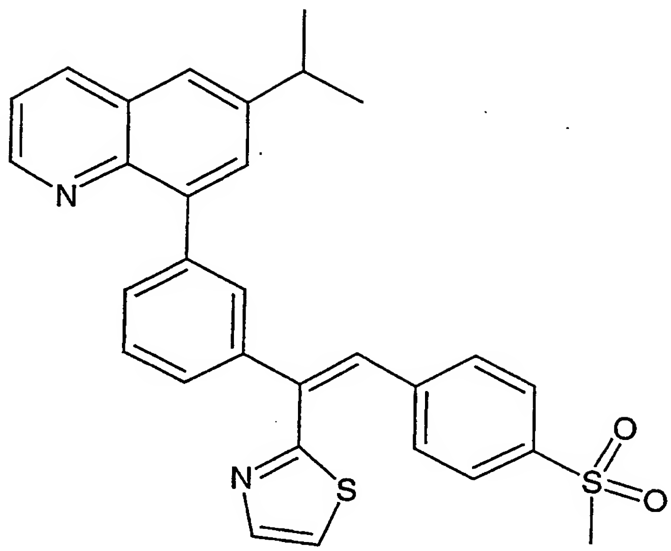
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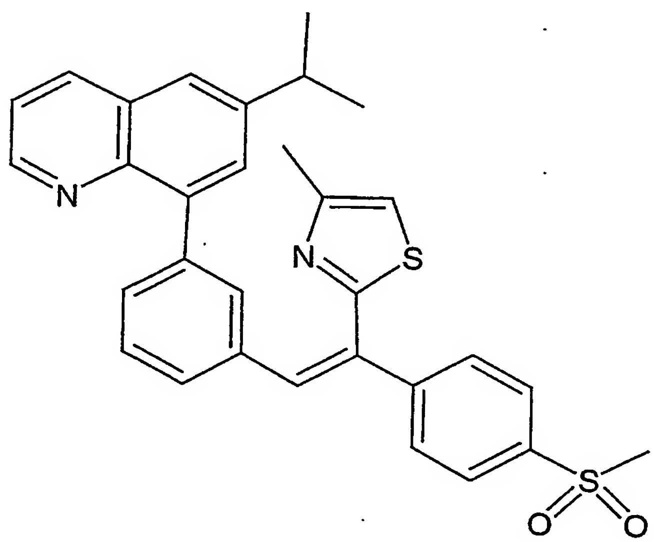
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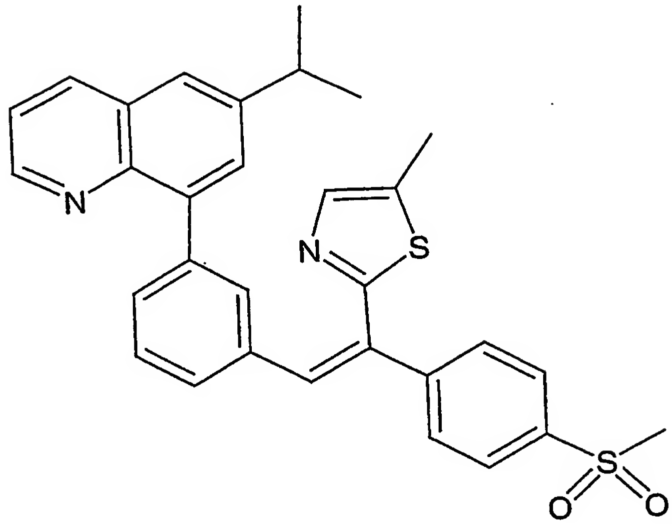

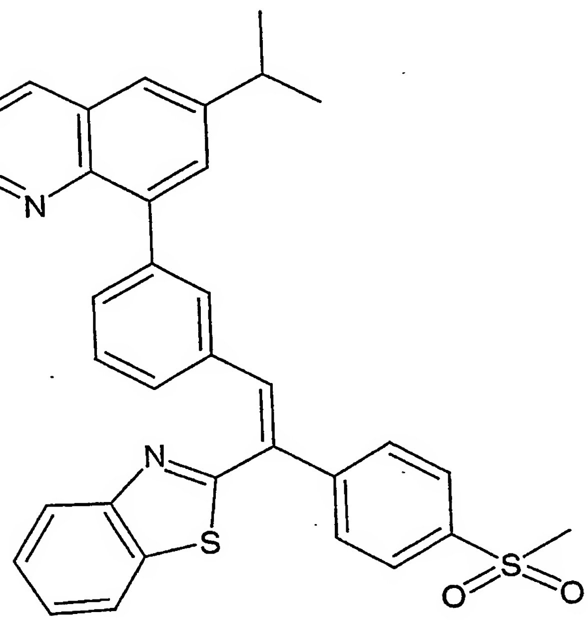

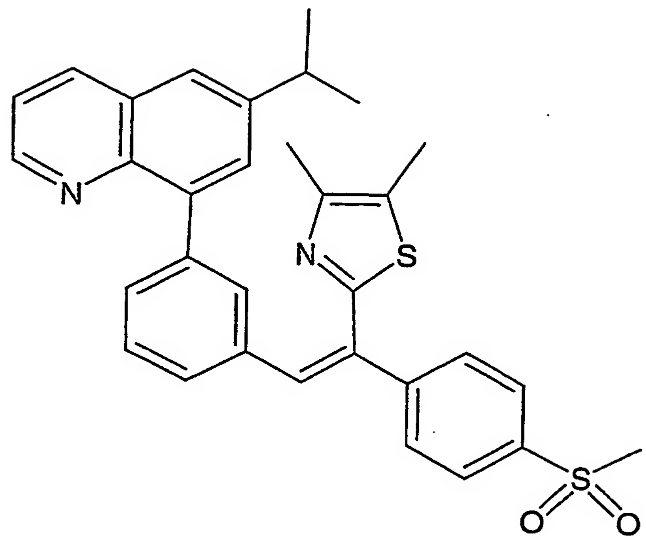
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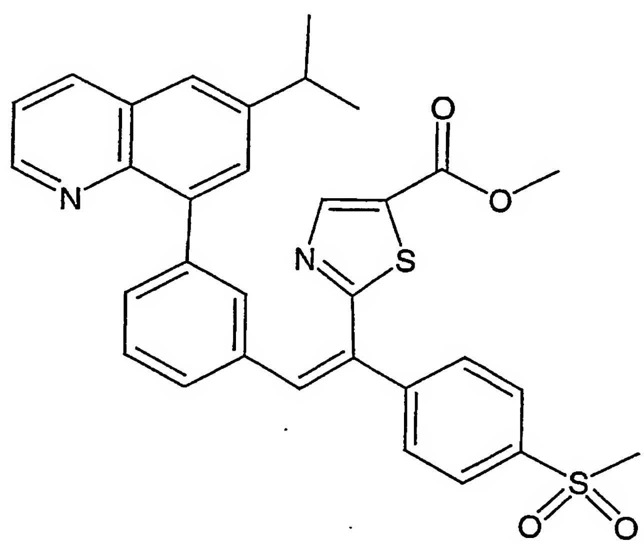
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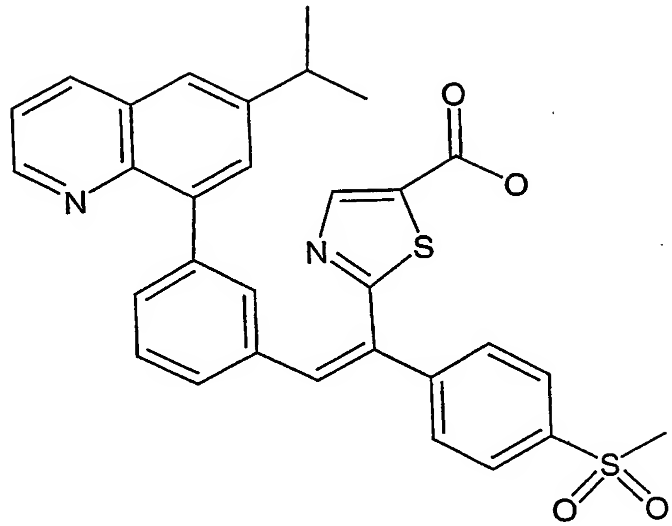

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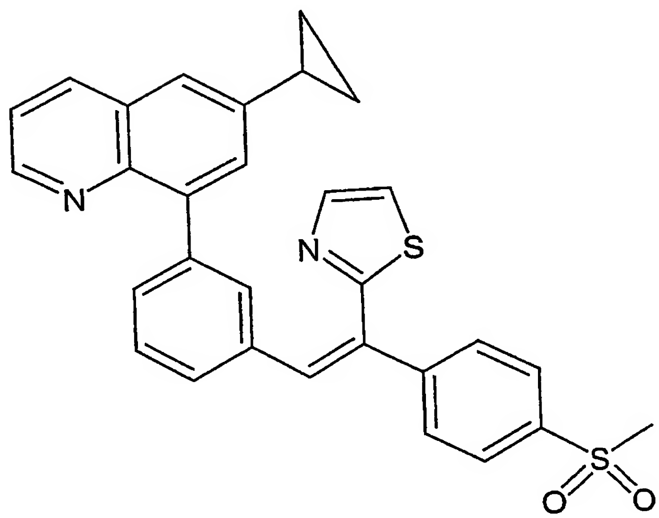

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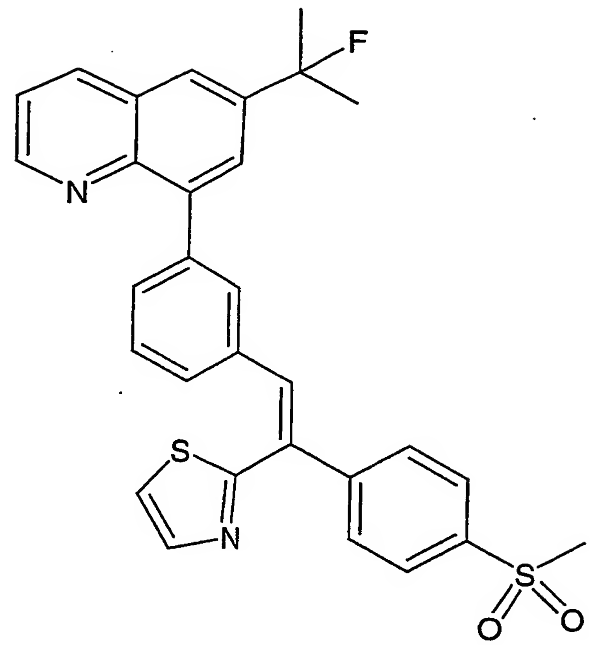
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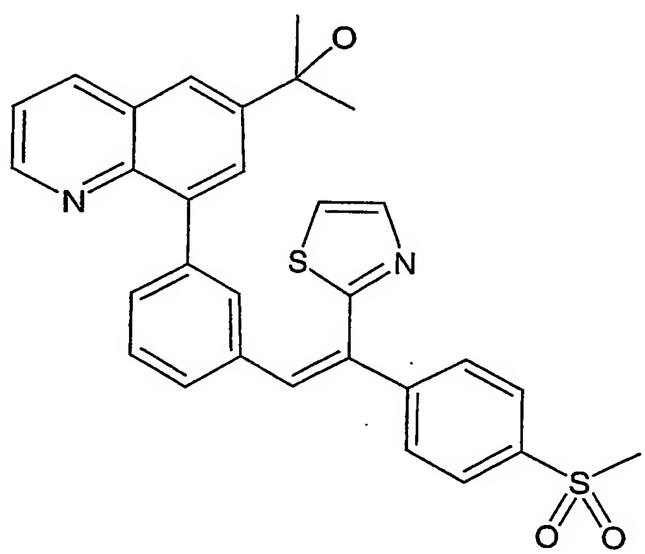
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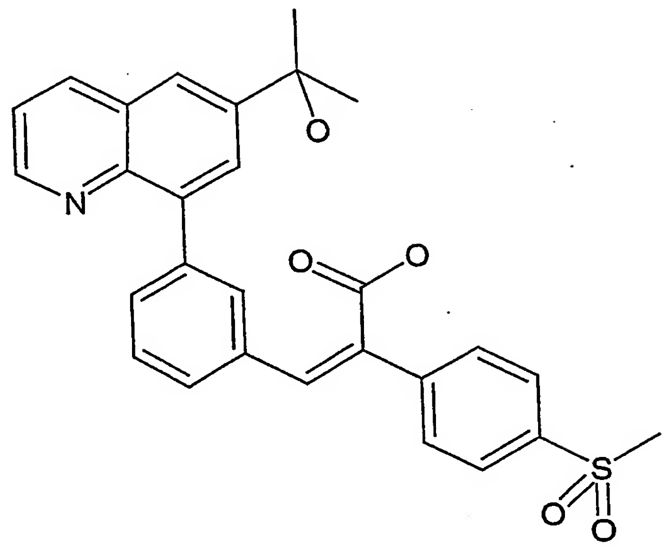

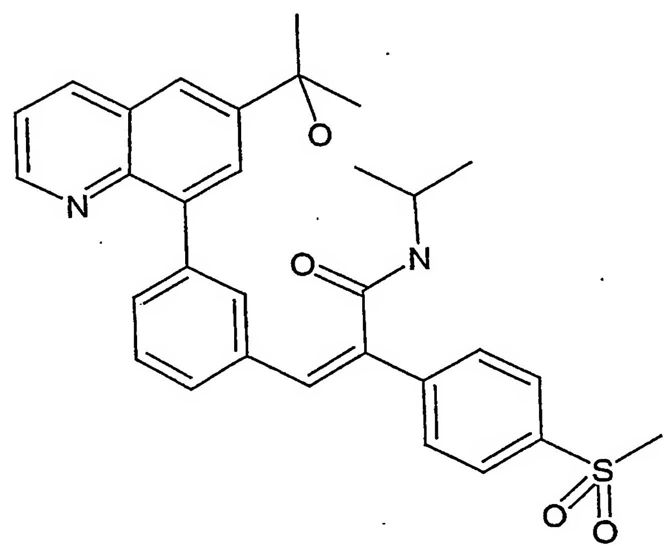

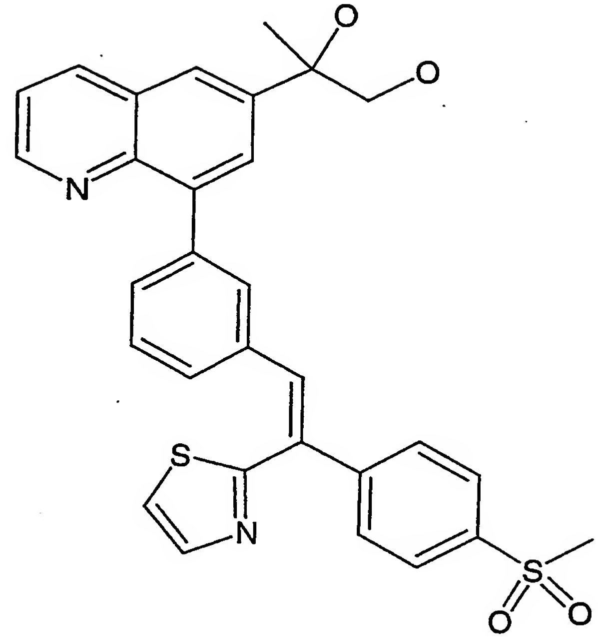

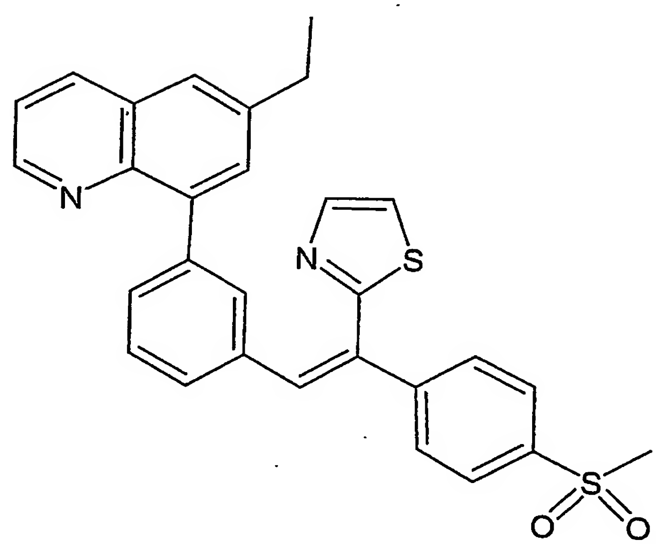

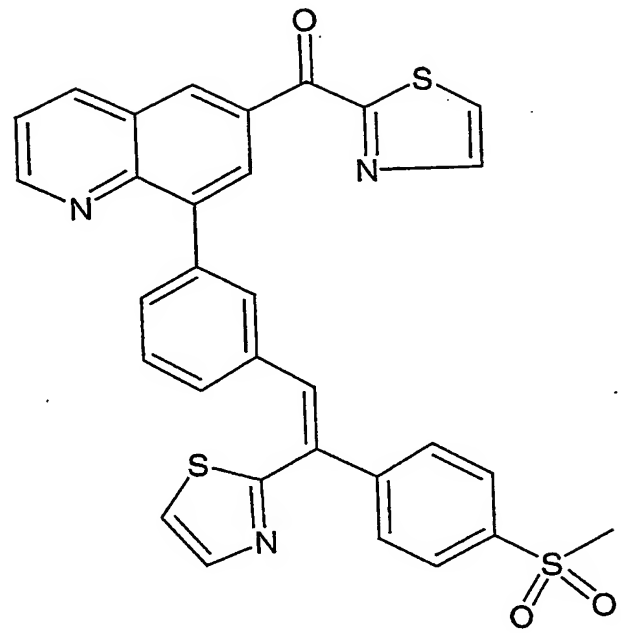

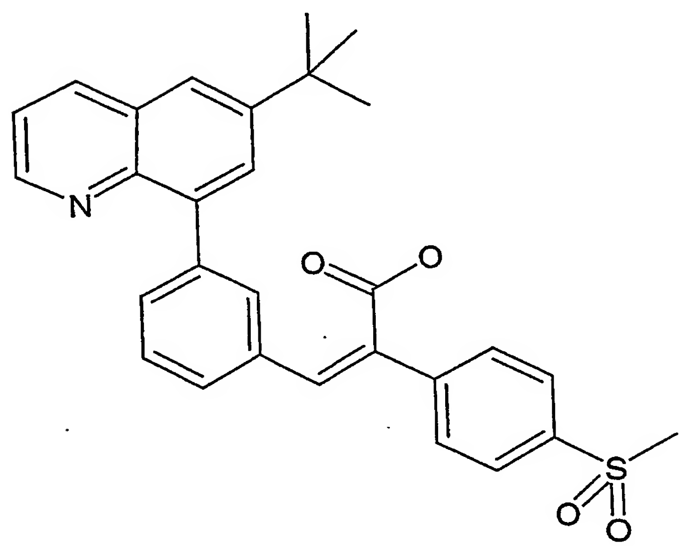

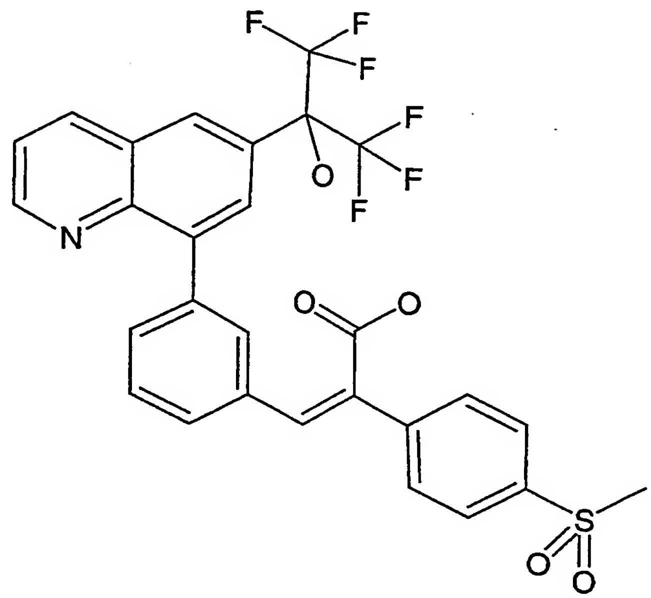

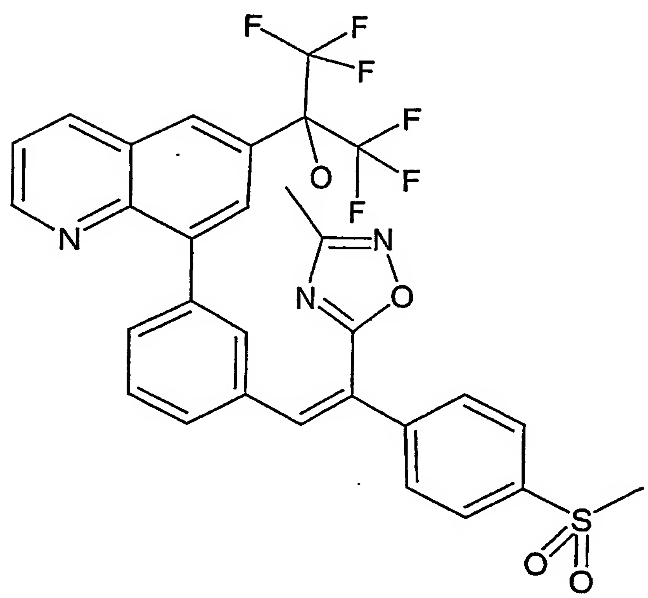

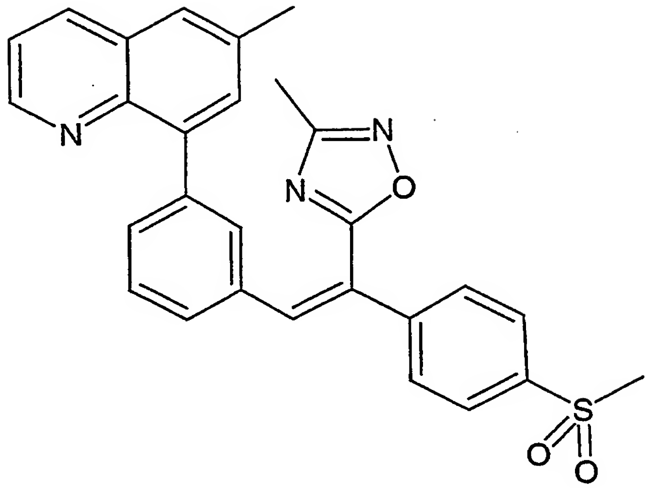

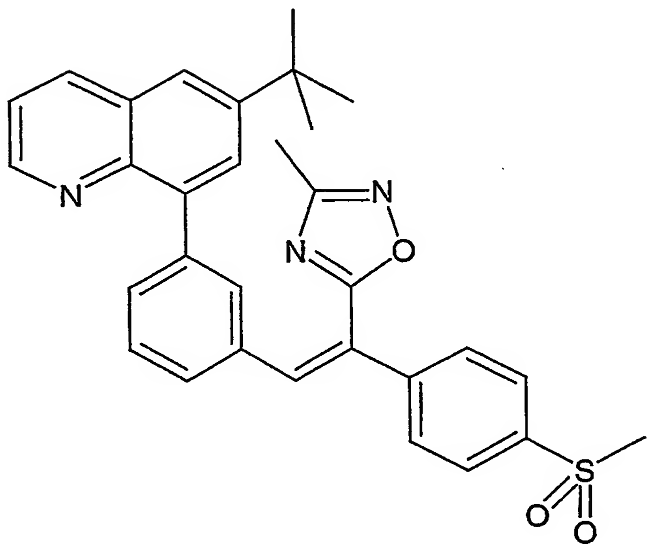

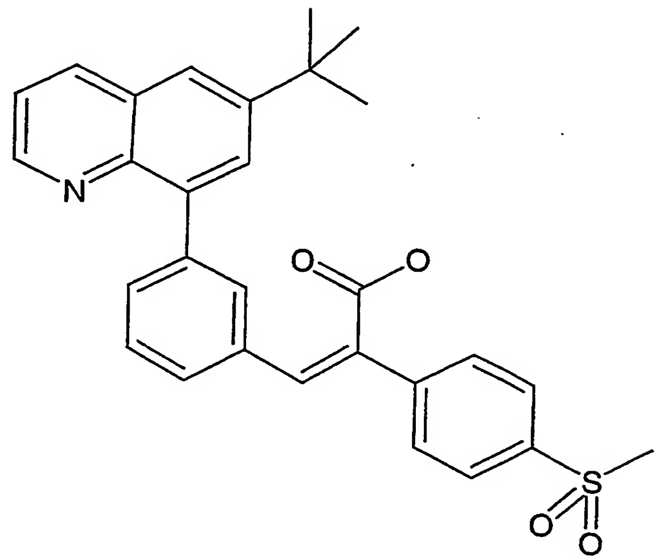

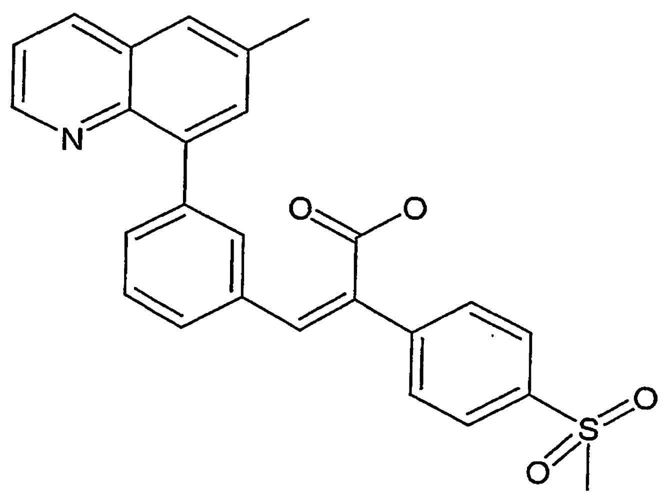

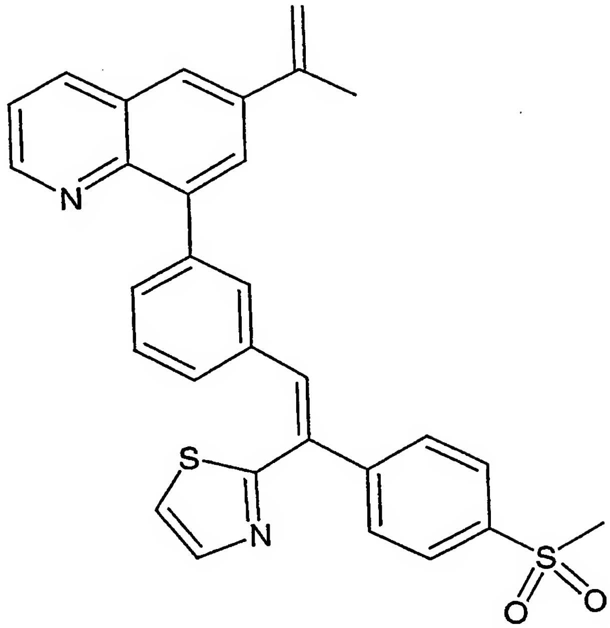

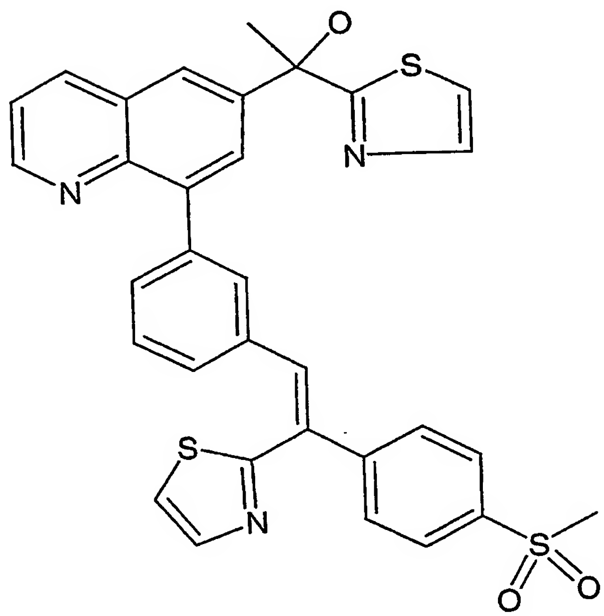

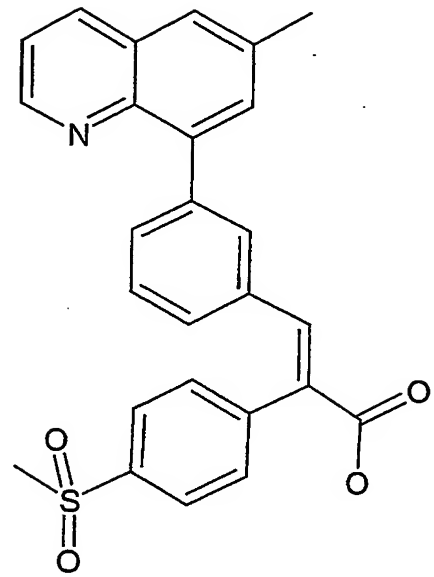
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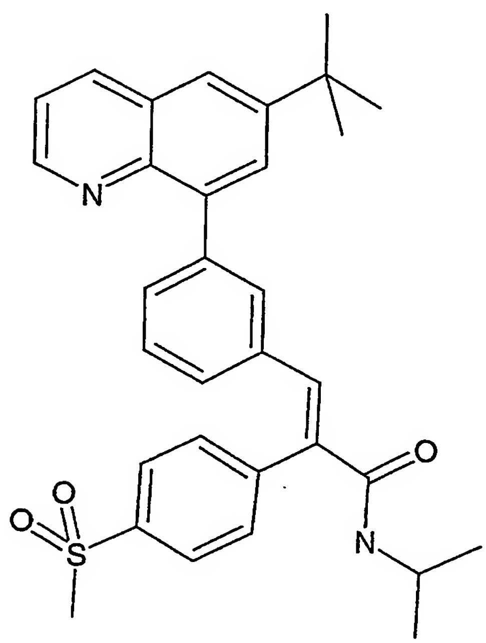
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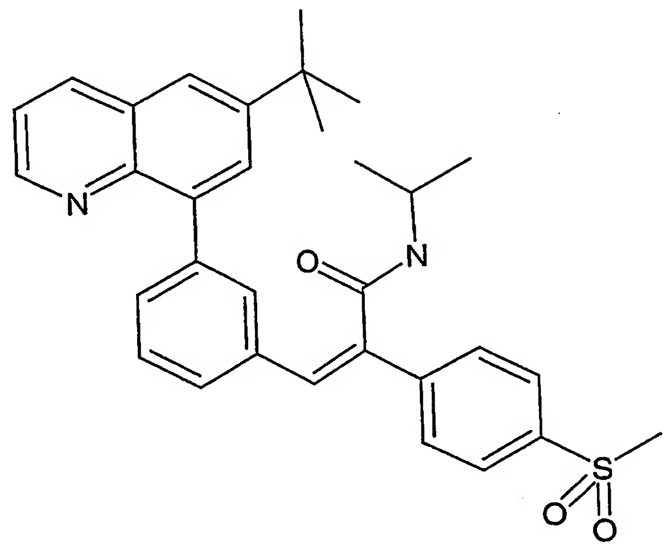
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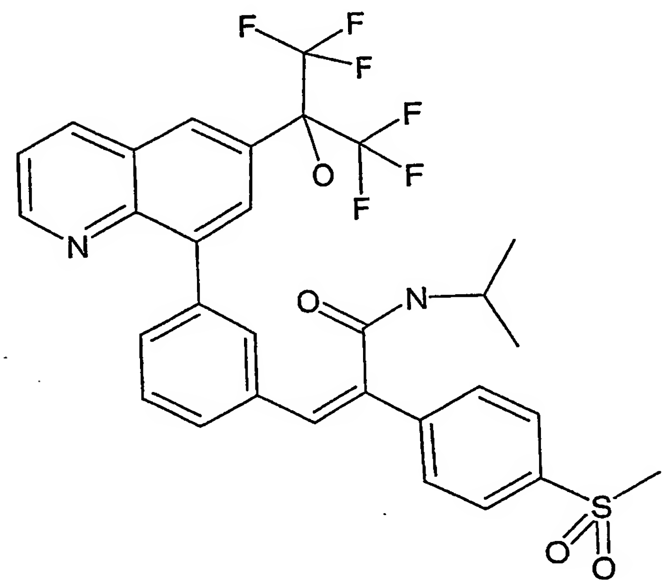
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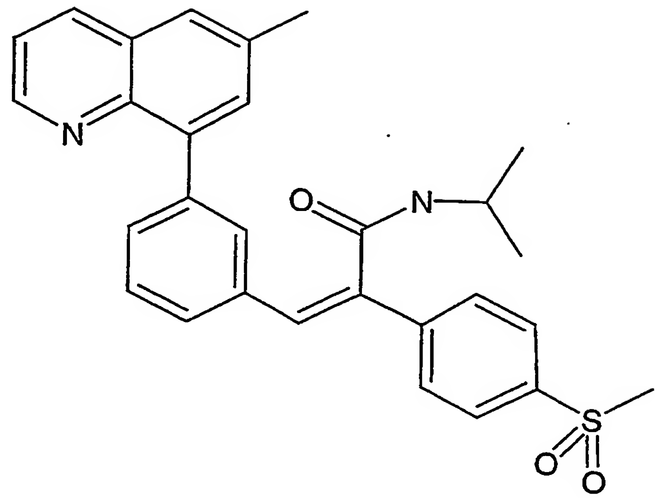
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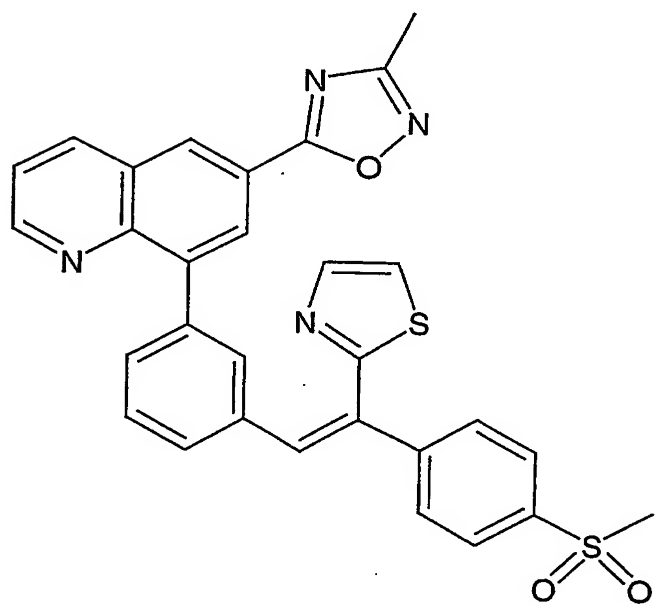
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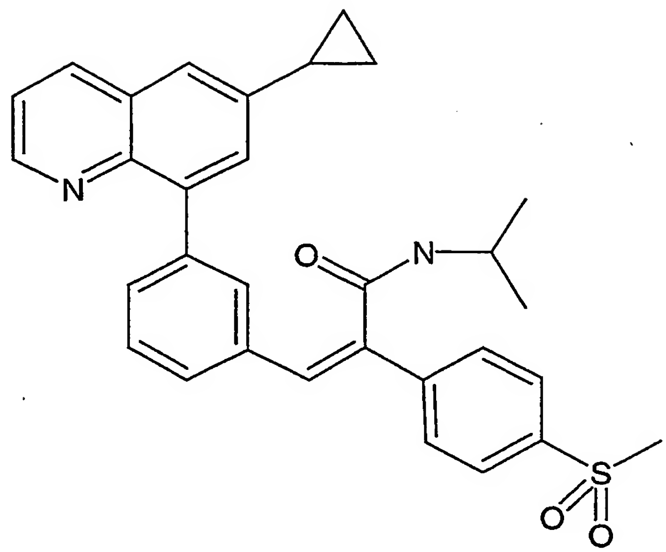
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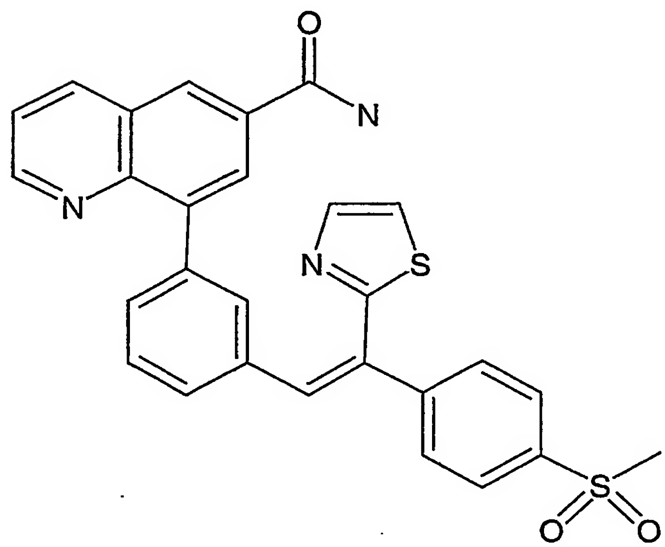
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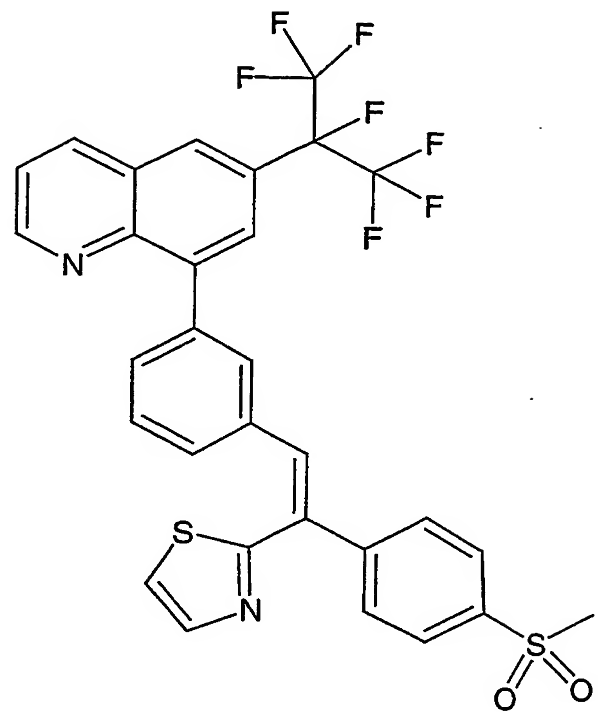

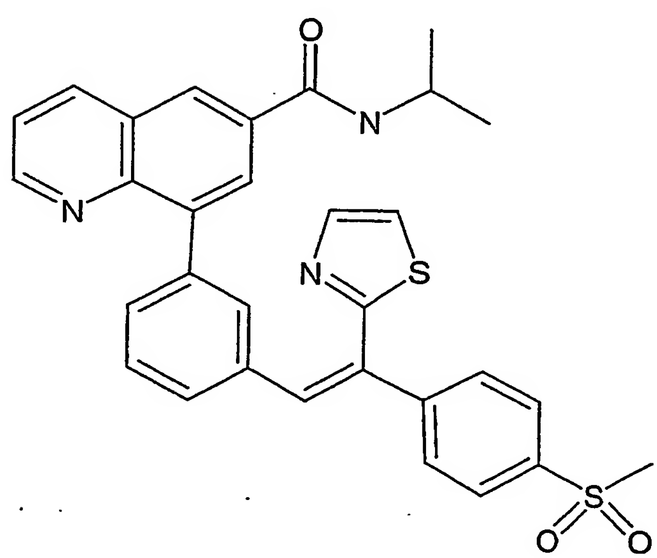

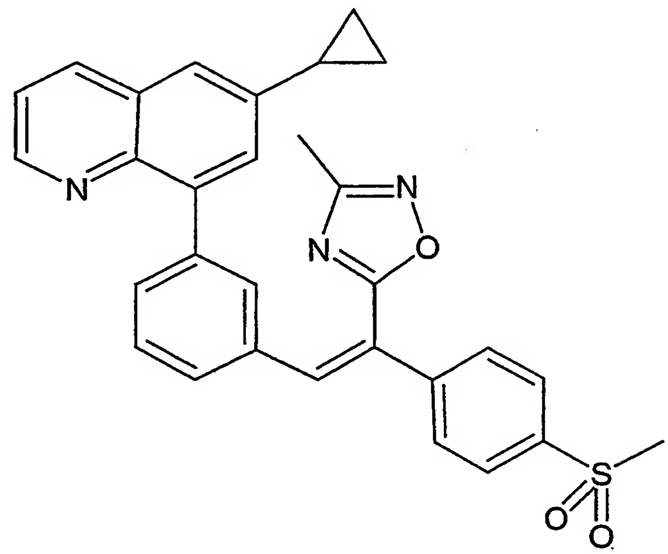
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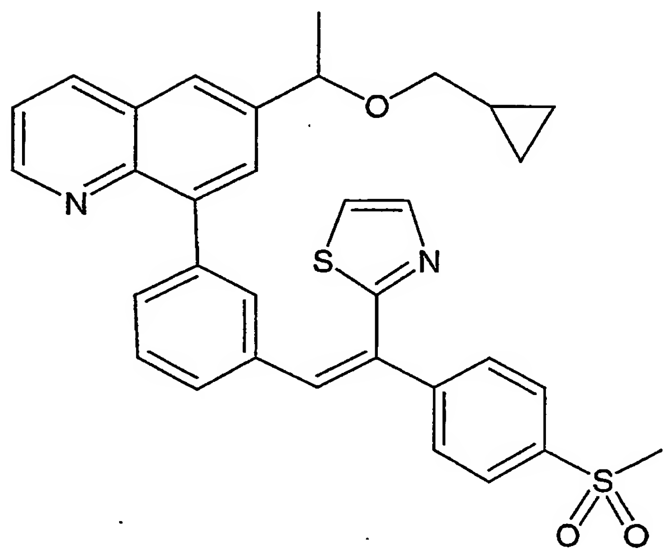
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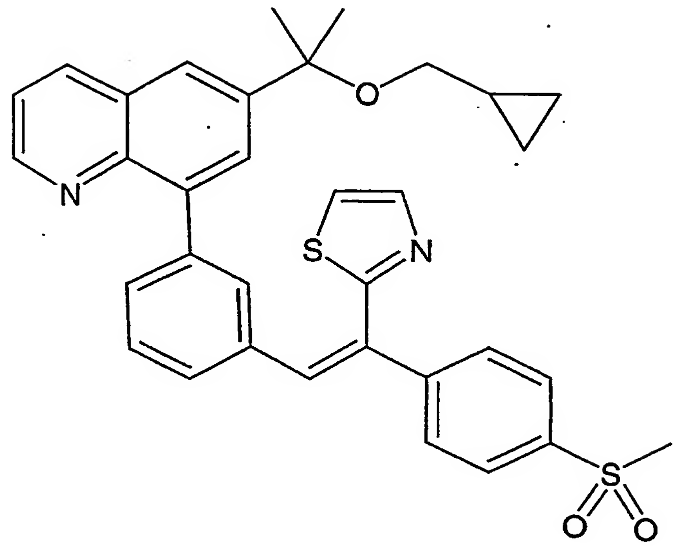
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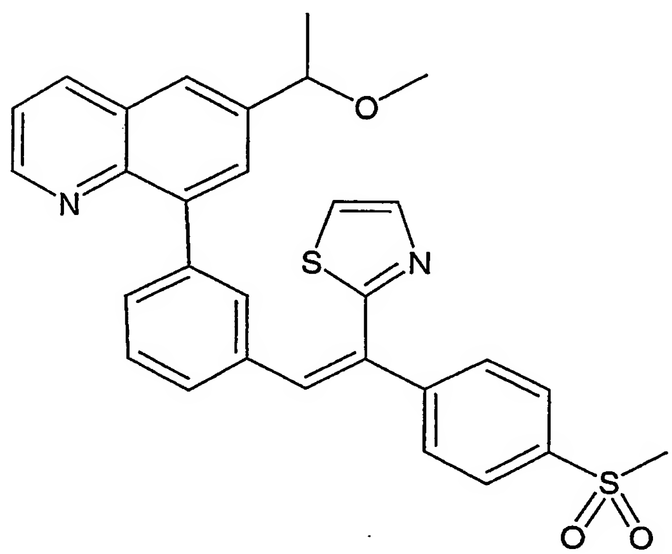
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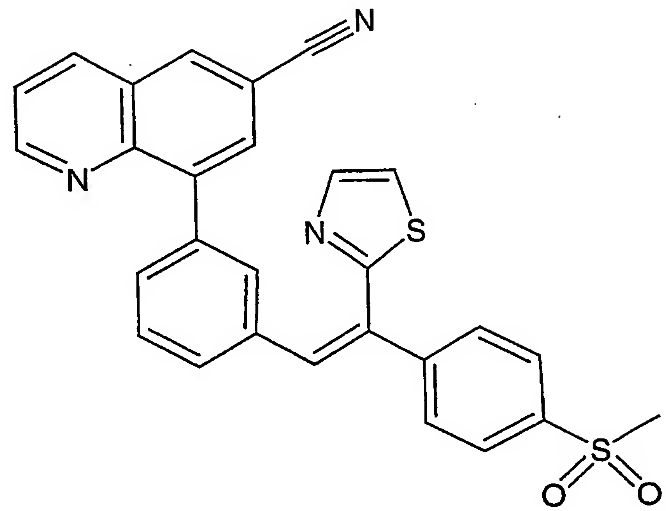
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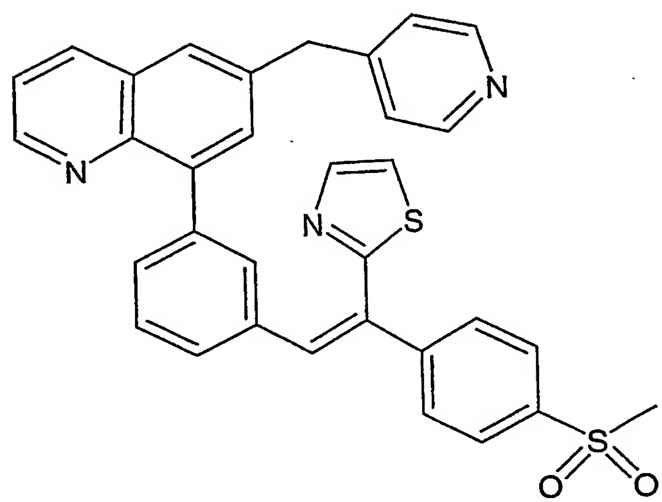
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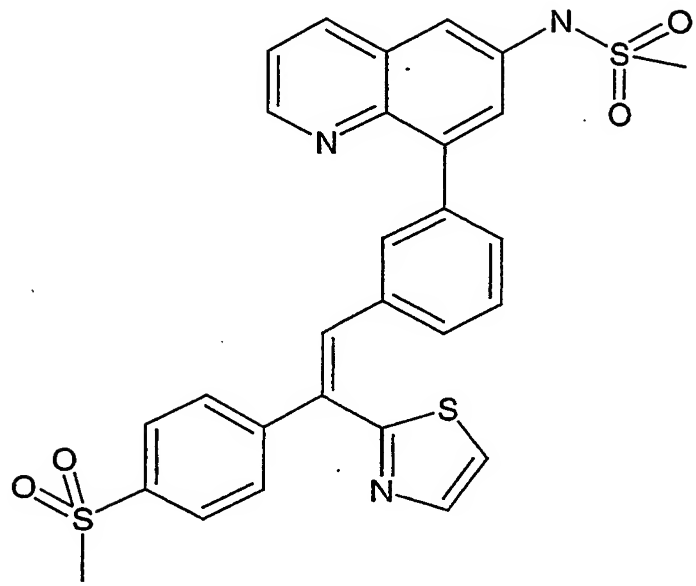
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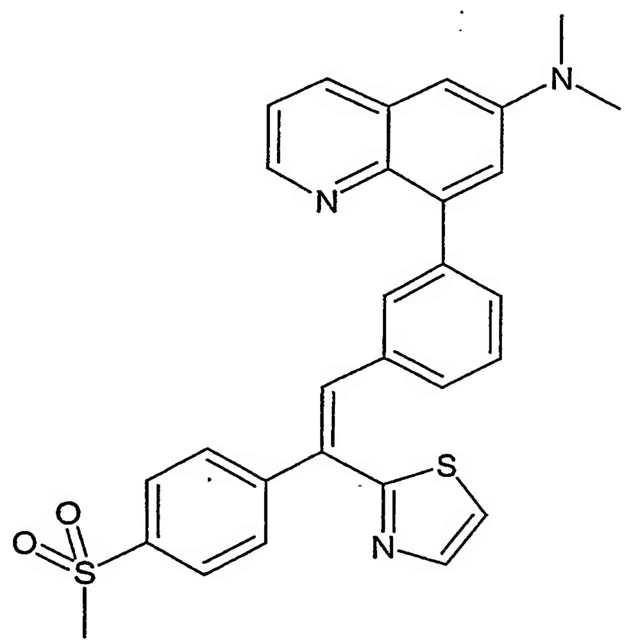
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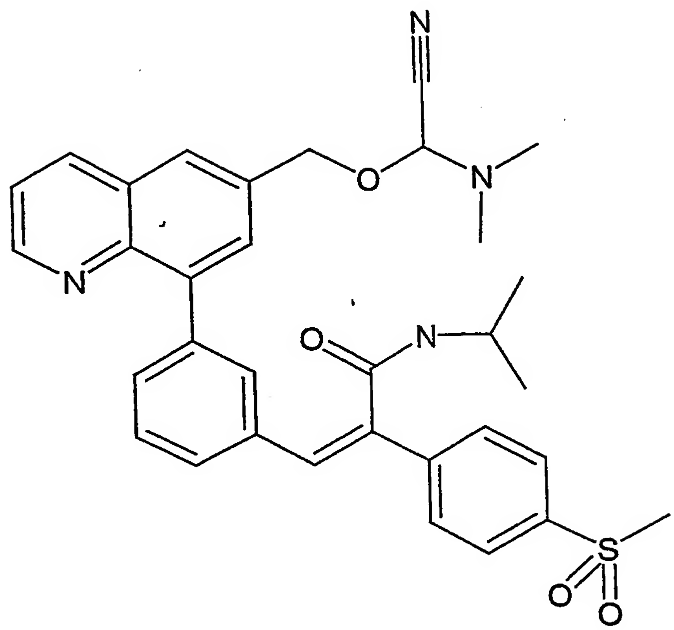

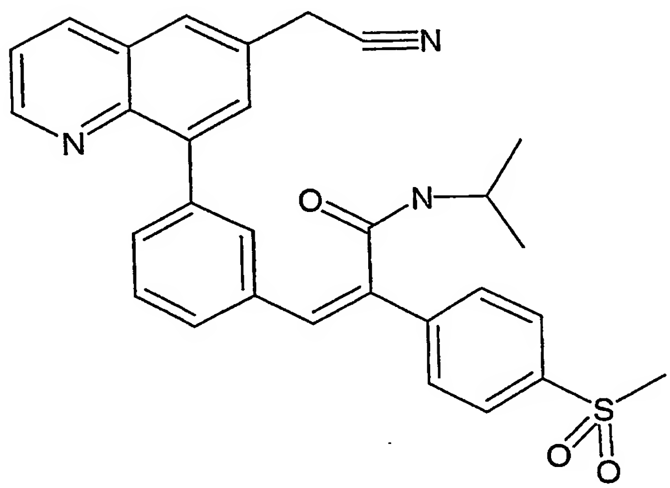

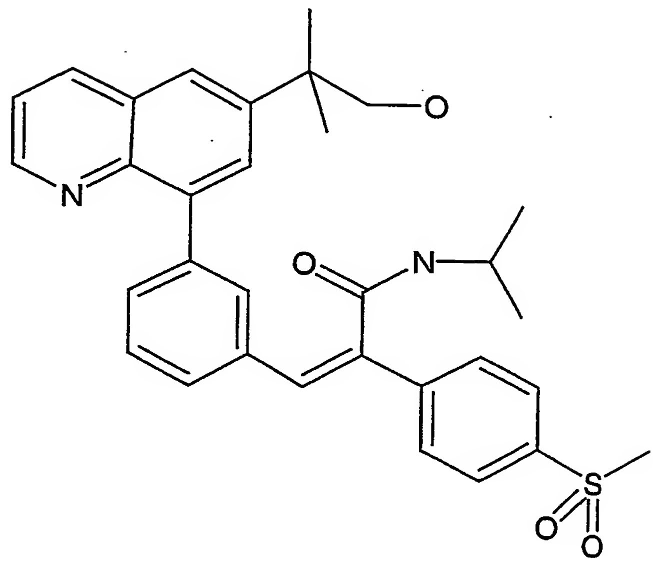
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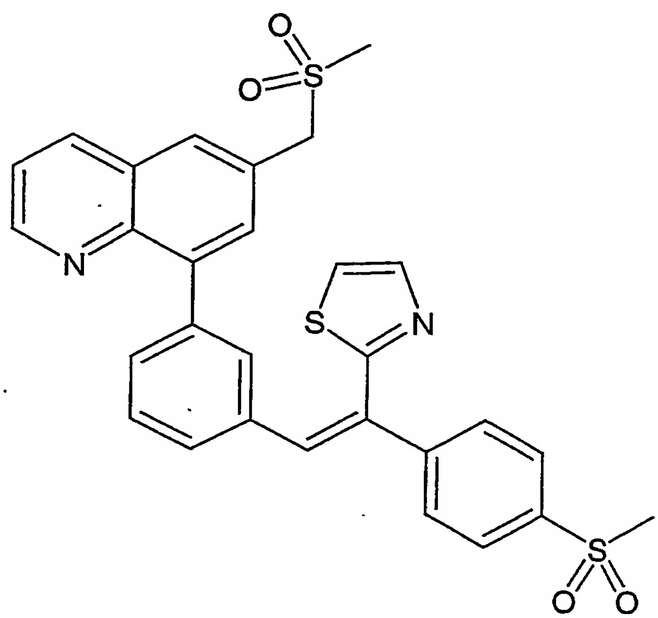
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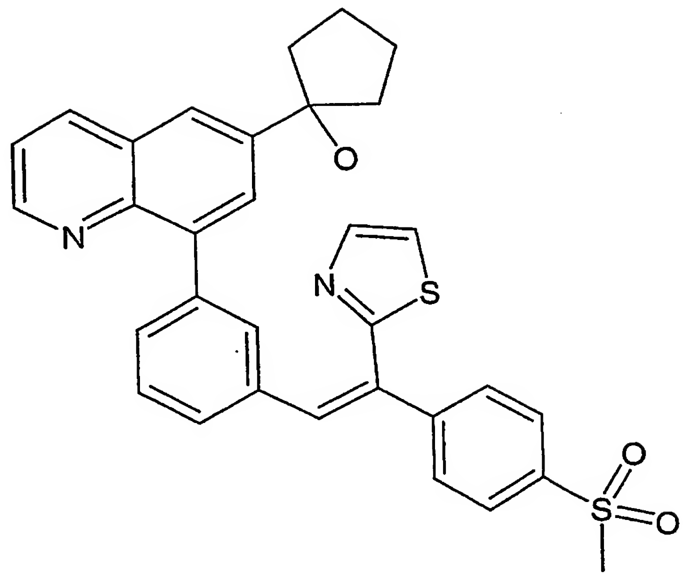
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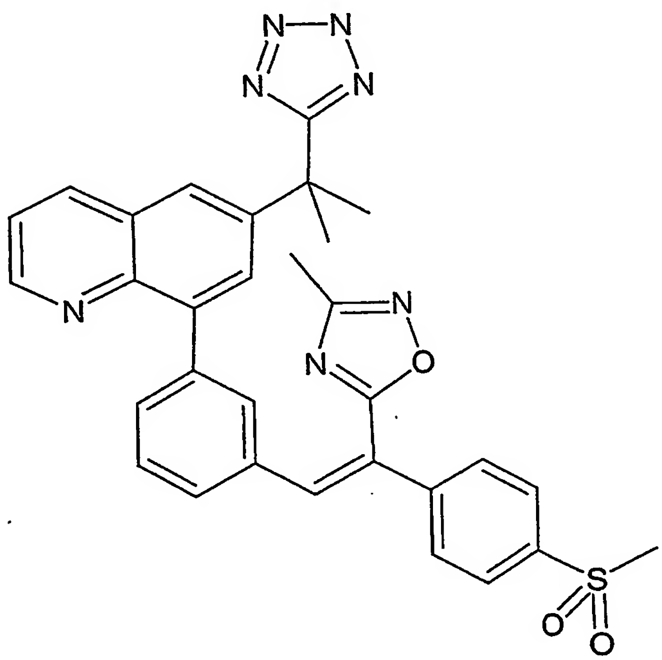
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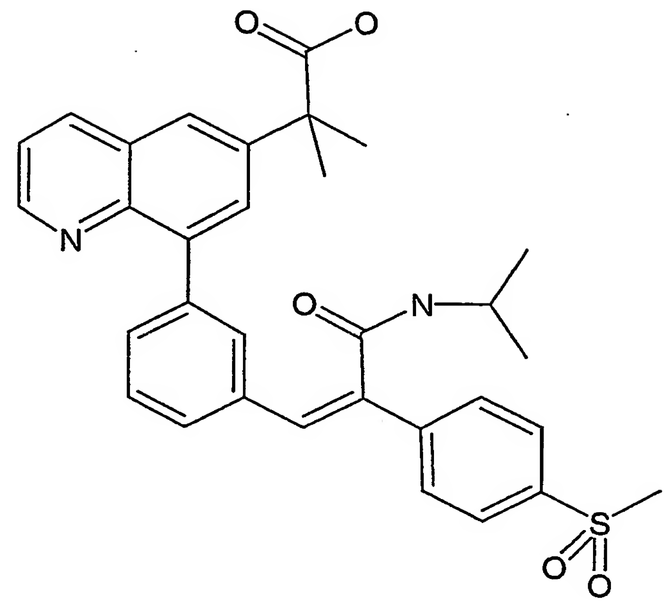

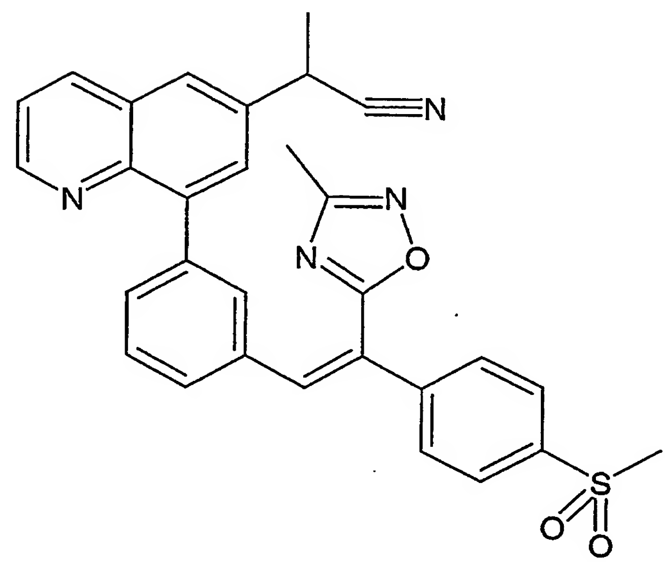

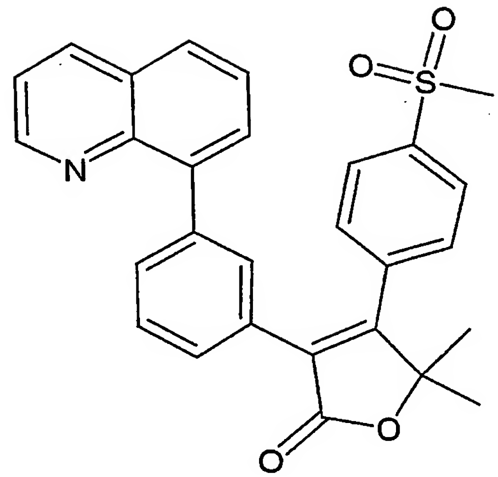

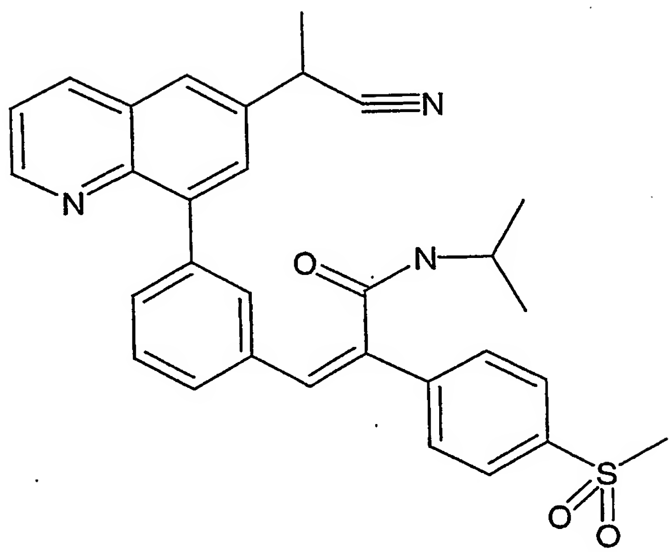

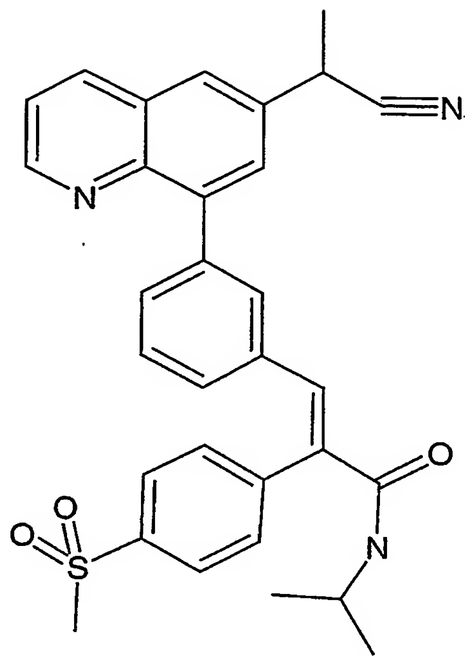

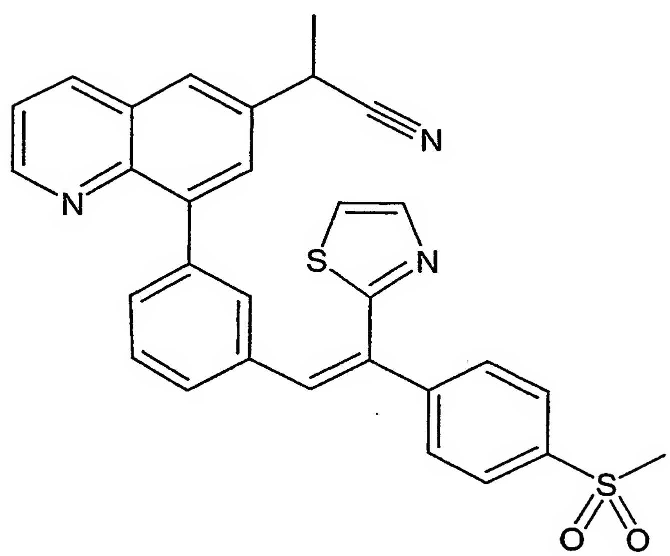

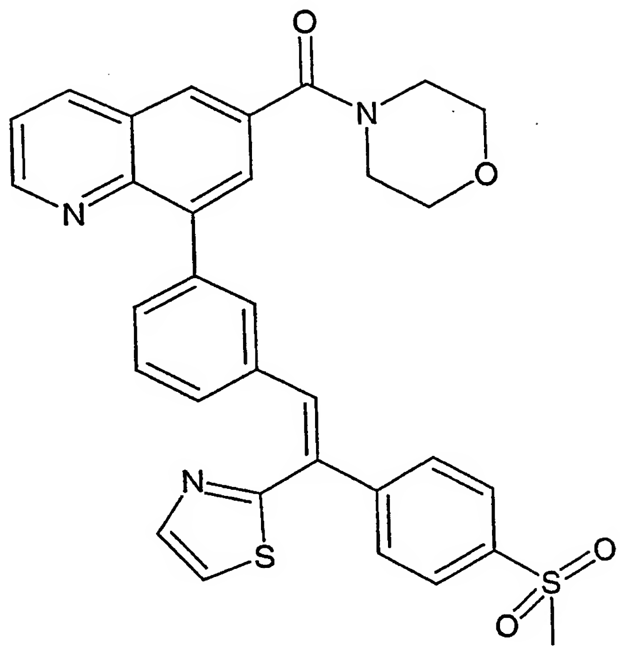

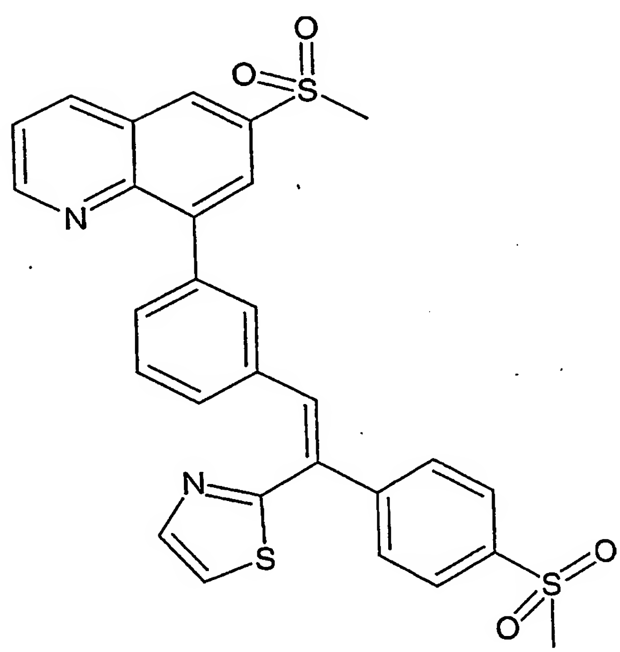

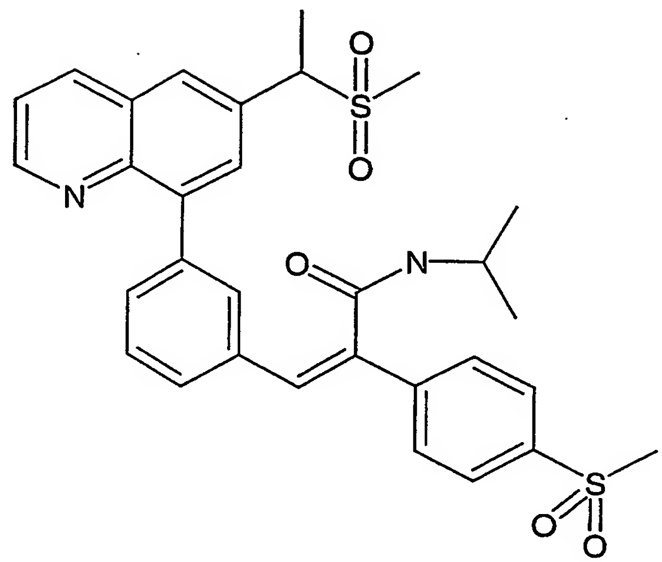

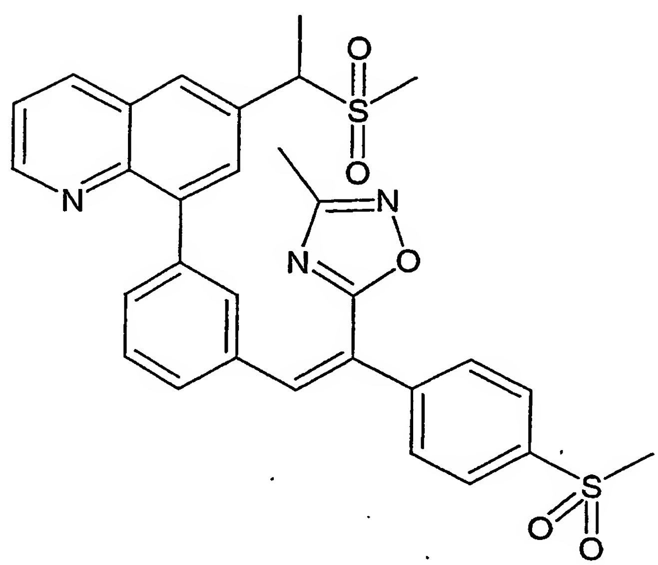

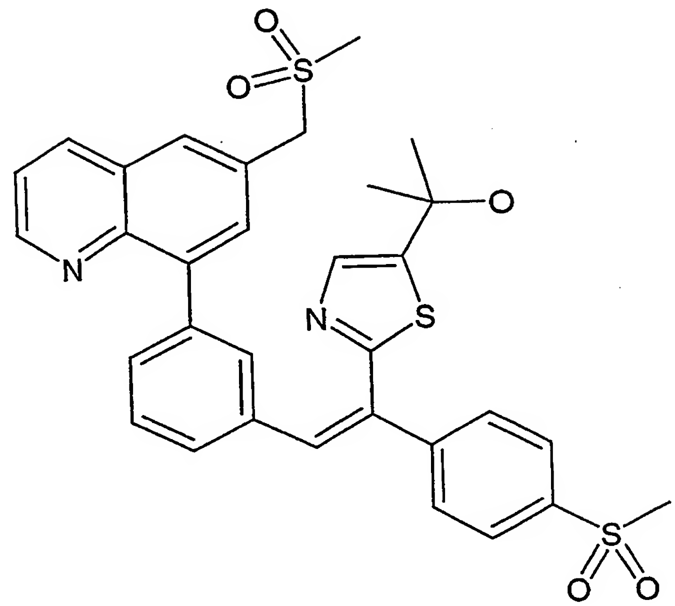

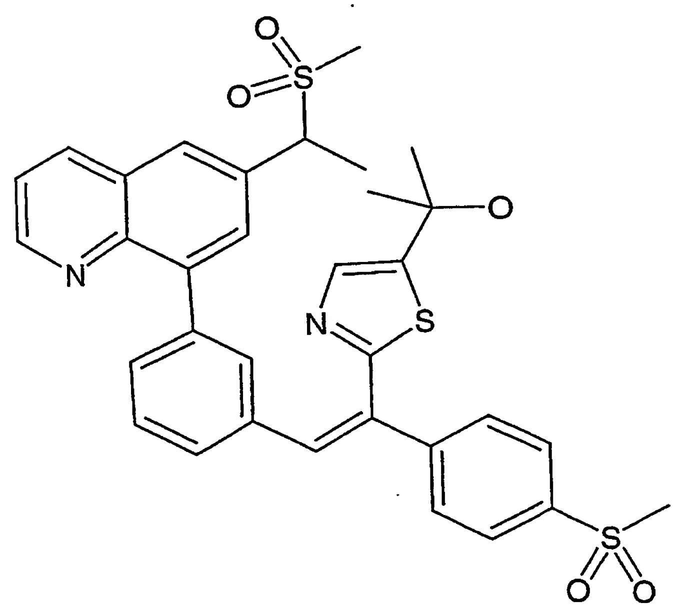

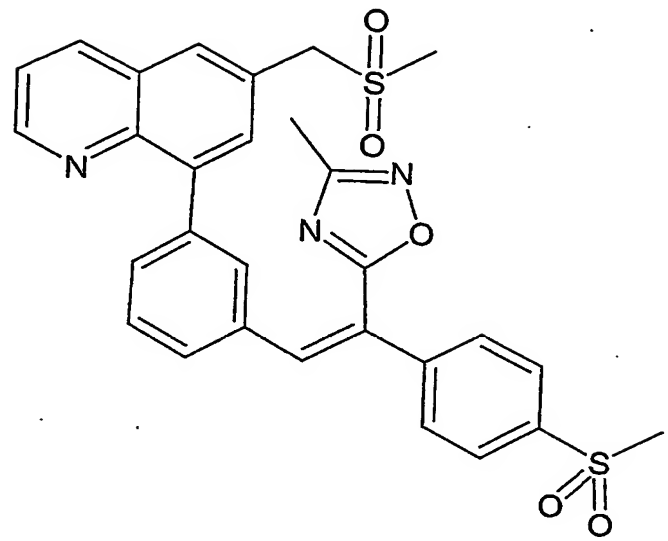
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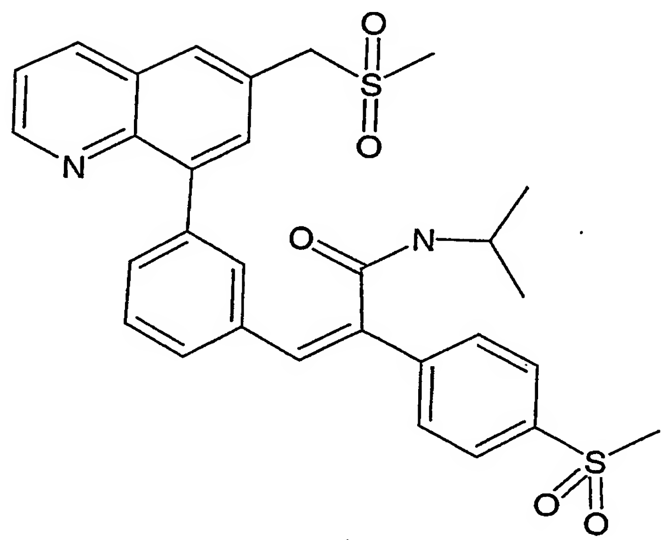
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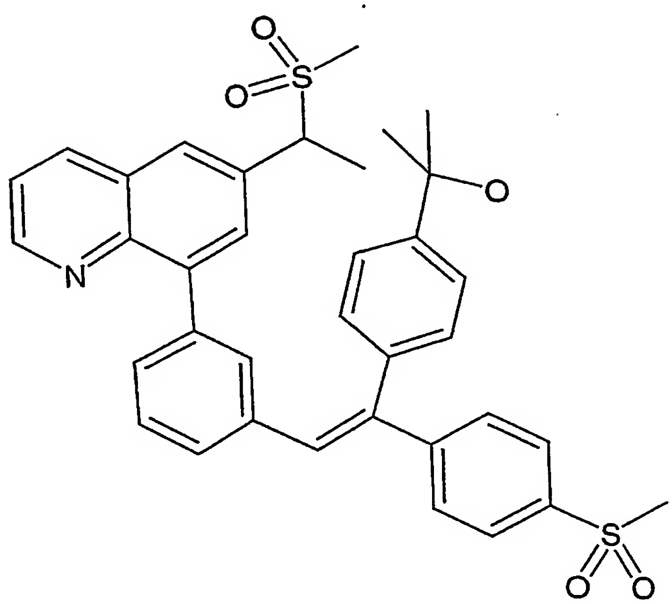
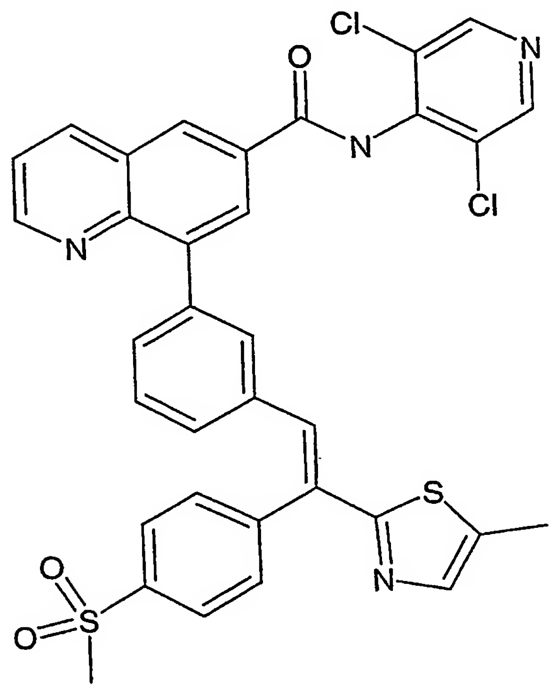
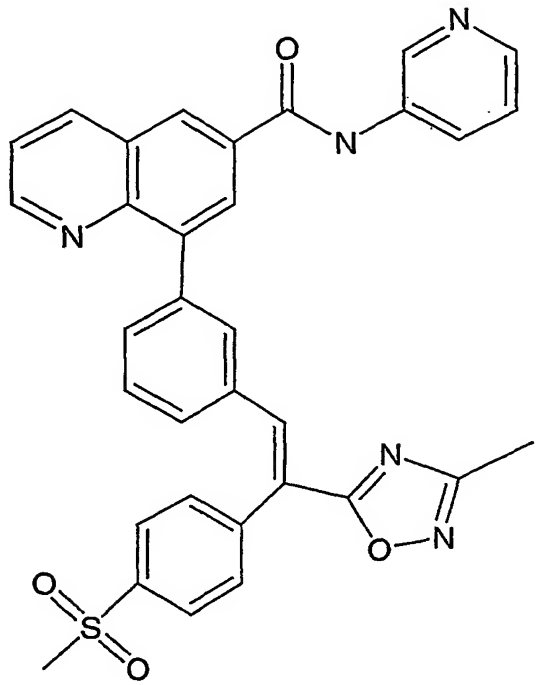






Salts of the Examples

As discussed above, pharmaceutically acceptable salts are often desirable. Examples of such salts are described below:

General Method for Salt Preparation

Salts of the compounds of this invention that are basic may be prepared in several ways:

a) The compound is dissolved in acceptable solvent such as ethyl acetate. An acceptable acid such as hydrochloric acid in an acceptable solvent such as 1,4-

dioxane is then added. The precipitated salt slurry is aged and the salt is then isolated by filtration.

b) The compound and an acceptable acid such as benzenesulfonic acid are dissolved in an acceptable solvent such as isopropyl acetate or in a mixture of solvents such as isopropyl acetate and methanol. The salt may then be isolated by concentration or a solvent switch, leading to precipitation, followed by filtration. The more stable crystal form of the salt may be obtained by equilibration of the precipitated salt slurry by heating and aging prior to filtration. Seed crystals from previous batches may also be added prior to equilibration of the salt slurry, to initiate the process of crystallization and equilibration.

SULFURIC ACID SALT OF THE EXAMPLE 14 COMPOUND

The sulfuric acid salt of the example 14 compound was prepared by dissolving the compound (1.00 equiv) in refluxing ethyl acetate. After cooling to room temperature, sulfuric acid (1.04 equiv) was added slowly, while stirring. The resulting suspension was stirred a further 40 minutes and the solid was isolated by filtration and washed with ethyl acetate to give the sulfuric acid salt of the example 14 compound.

1H NMR (500 MHz, acetone-d6): d 9.45 (d, 1H), 9.23 (d, 1H), 8.65 (d, 1H), 8.25 (d, 1H), 8.16 (dd, 1H), 8.10 (s, 1H), 7.99 (d, 2H), 7.80 (d, 2H), 7.60 (d, 1H), 7.49 (s, 1H), 7.45 (t, 1H), 7.30 (d, 1H), 3.09 (s, 3H), 2.77 (s, 3H), 2.33 (s, 3H), 2.01 (s, 6H).

METHANESULFONIC ACID SALT OF THE EXAMPLE 14 COMPOUND

The methanesulfonic acid salt of the example 14 compound was prepared by dissolving the compound (1.0 equiv) in refluxing ethyl acetate. After cooling to room temperature, methanesulfonic acid (1.1 equiv) was added slowly, while stirring. The resulting suspension was stirred, allowed to concentrate by evaporation and the solid was isolated by filtration and washed with ether to give the methanesulfonic acid salt of the example 14 compound.

1H NMR (500 MHz, acetone-d6): d 9.45 (d, 1H), 9.32 (d, 1H), 8.70 (s, 1H), 8.27 (s, 1H), 8.22 (t, 1H), 8.11 (s, 1H), 7.99 (d, 2H), 7.78 (d, 2H), 7.61 (d, 1H), 7.49 (m, 2H), 7.35 (d, 1H), 3.09 (s, 3H), 2.78 (s, 3H), 2.33 (s, 3H), 2.01 (s, 6H).

p-TOLUENESULFONIC ACID SALT OF THE EXAMPLE 14 COMPOUND

The p-toluenesulfonic acid salt of the example 14 compound was prepared by dissolving the compound (1.0 equiv) in refluxing ethyl acetate. After cooling to room temperature, p-toluenesulfonic acid (1.1 equiv) in ethyl acetate was added slowly. The solution was concentrated and the suspension was aged with stirring and periodic sonication at room temperature for 3 days. The solid was then isolated by filtration and washed with ethyl acetate to give the p-toluenesulfonic acid salt of the example 14 compound).

mp 184-185 °C.

1H NMR (500 MHz, acetone-d6): d 9.58 (d, 1H), 9.22 (d, 1H), 8.63 (s, 1H), 8.23 (d, 1H), 8.16 (m, 1H), 8.03 (s, 1H), 7.94 (d, 2H), 7.73 (d, 2H), 7.55 (m, 3H), 7.45 (s, 1H), 7.40 (t, 1H), 7.27 (d, 1H), 7.12 (d, 2H), 3.07 (s, 3H), 2.75 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 2.01 (s, 6H).

2-NAPHTHALENESULFONIC ACID SALT OF THE EXAMPLE 14 COMPOUND

The 2-naphthalenesulfonic acid salt of the example 14 compound was prepared by dissolving the compound (1.0 equiv) in refluxing ethyl acetate. After cooling to room temperature, 2-naphthalenesulfonic acid (1.1 equiv) in ethyl acetate was added slowly, followed by ethanol. Toluene was then added to the solution, followed by concentration. More toluene was then added and the suspension was aged with stirring and periodic sonication at room temperature for 24h. The solid was then isolated by filtration and washed with toluene to give the 2-naphthalenesulfonic acid salt of the example 14 compound.

mp 202-204 °C.

1H NMR (500 MHz, acetone-d6): d 9.64 (d, 1H), 9.30 (d, 1H), 8.67 (d, 1H), 8.25 (d, 1H), 8.23 (m, 1H), 8.16 (s, 1H), 7.99 (s, 1H), 7.91 (d, 2H), 7.87 (m, 2H), 7.82 (d, 1H), 7.72 (dd, 1H), 7.68 (d, 2H), 7.54 (d, 1H), 7.52 (m, 2H), 7.43 (brs, 1H), 7.37 (t, 1H), 7.22 (d, 1H), 3.03 (s, 3H), 2.76 (s, 3H), 2.33 (s, 3H), 2.02 (s, 6H).

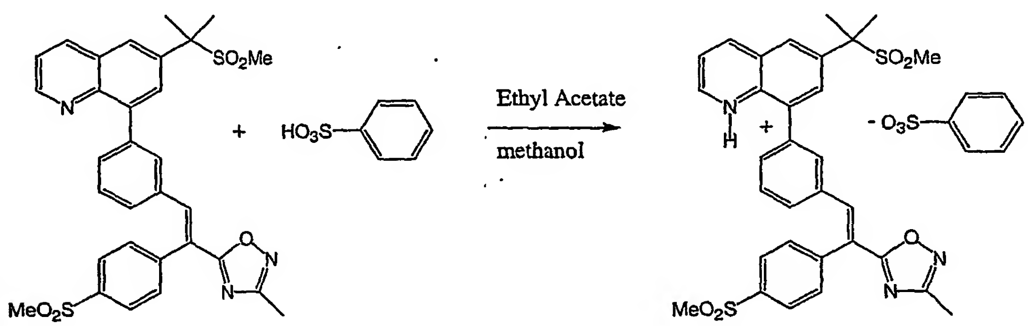
HYDROCHLORIDE SALT OF THE EXAMPLE 43 COMPOUND

The hydrochloride salt of the example 43 compound was prepared by dissolving the compound (1.0 equiv) in ethyl acetate with heating and sonication. After cooling the solution to room temperature, HCl in 1,4-dioxane (4M, 1.0 equiv) was added while stirring. The suspension was stirred for a further 5 minutes and the solid was isolated by filtration to give the mono-hydrochloride salt of the example 43 compound.

BENZENESULFONIC ACID SALT OF THE EXAMPLE 14 COMPOUND

The benzenesulfonic acid salt of the Example 14 compound is available in two crystalline forms ("Form A" and "Form B"). The forms are produced by the following procedures:

Salt Formation



Form A

To a slurry of the Example 14 compound (1 equiv) in ethyl acetate was added benzenesulfonic acid (1-1.2 equiv). Other esters may be used in place of ethyl acetate. Methanol was added and the resulting mixture was heated until the solid dissolved. Other alcohols such as ethanol or propanol may be used in place of the methanol.

The resulting solution was filtered and concentrated. The product crystallized during concentration. The resulting mixture was diluted with ethyl acetate and aged. The yellow solid was collected by filtration.

HPLC indicated a 1:1 molar ratio of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(*E*)-2-[3-methyl-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline and benzenesulfonic acid.

m.p. by DSC: 193°C.

The X-ray Powder Diffraction ("XRPD") Spectrogram for the Form A is shown in Fig. 1. The identifying peaks are tabulated below and shown in Fig. 4.

Peaks Identifying **Form A** Polymorph (°2Theta)
10.0
19.5
21.4
22.4
30.5

Form B

To a slurry of the Example 14 compound (1 equiv) in a mixture of isopropyl acetate (i-PrOAc) and methanol (1:1) was added benzenesulfonic acid (1-1.2 equiv). Other esters may be used in place of i-PrOAc and other alcohols such as ethanol or propanol may be used in place of methanol. The mixture was aged at 20 - 50 °C until the solids dissolved. The resulting solution was filtered and distilled while the volume was maintained by addition of a 9:1 (v/v) mixture of i-PrOAc/methanol. The product crystallized during the distillation.

The resulting mixture was aged at 20 – 70 °C for 2-10 h to ensure complete formation of Form B. The resulting off-white solid was isolated by filtration and dried.

HPLC indicated a 1:1 molar ratio of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(*E*)-2-[3-methyl-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline and benzenesulfonic acid.

m.p. by DSC: 210°C

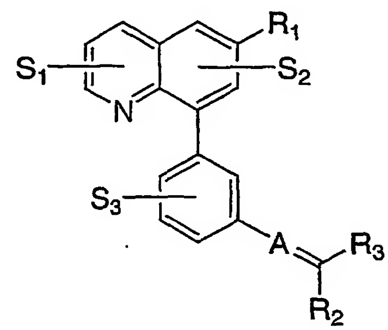
The XRPD Spectrogram for the Form B is shown in Fig. 2. The identifying peaks are tabulated below and shown in Fig. 5. The spectra are compared in Fig. 3 with the identifying peaks pointed out by arrows.

Peaks Identifying **Form B** Polymorph (°2Theta)
14.4
17.7
20.0
20.2
23.7
28.9

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

S_1, S_2, and S_3 are independently H, -OH, halogen, -C_1-C_6alkyl, -NO_2, -CN, or -C_1-C_6alkoxy, wherein the alkyl and alkoxy groups are optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen or OH;

R_1 is a H, OH, halogen, or carbonyl group, -C_1-C_6alkyl group, -cycloC_3-C_6alkyl group, -C_1-C_6alkenyl group, -C_1-C_6alkoxy group, aryl group, heteroaryl group, -CN, -heterocycloC_3-C_6alkyl group, -amino group, -C_1-C_6alkylamino group, -(C_1-C_6alkyl)(C_1-C_6alkyl)amino group, -C_1-C_6alkyl(oxy)C_1-C_6alkyl group, -C(O)NH(aryl) group, -C(O)NH(heteroaryl) group, -SO_nNH(aryl) group, -SO_nNH(heteroaryl) group, -SO_nNH(C_1-C_6alkyl) group, -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl) group, -NH-SO_n-(C_1-C_6alkyl) group, -SO_n-(C_1-C_6alkyl) group, -(C_1-C_6alkyl)-O-C(CN)-dialkylamino group, or -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-aryloxy, -C_1-C_6alkoxy, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO_n-(C_1-C_6alkyl);

A is CH, C-ester, or C-R_4;

R_2 and R_3 independently is an aryl group, heteroaryl group, H, halogen, –CN, -C_1-C_6alkyl group, -heterocycloC_3-C_6alkyl, -C_1-C_6alkoxy group, carbonyl group, carbamoyl group, -C(O)OH, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl) group, or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO_2, -C(O)OH, -CN, N-oxide, -OH, or an aryl, heteroaryl, carbonyl, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -SO_n-(aryl), aryloxy, -heteroaryloxy, C_1-C_6alkoxy, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, amino, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl) substituent group, wherein each substituent group independently is optionally substituted with -OH, C_1-C_6alkoxy, -C_1-C_6alkyl, -cycloC_3-C_6alkyl, aryloxy, -C(O)OH, -C(O)O(C_1-C_6alkyl), halogen, -NO_2, -CN, -SO_n-(C_1-C_6alkyl), or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl);

one of R_2 and R_3 must be an aryl or heteroaryl, optionally substituted;

when R_2 and R_3 are both an aryl or heteroaryl, then R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system;

R_4 is an aryl group, -C_1-C_6alkyl group, heteroaryl group, –CN, carbonyl, carbamoyl group, -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl) group, -C(O)N(C_0-C_6alkyl)(C_0-C_6alkyl) group, or -C_1-C_6alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a carbonyl, -CN, halogen, -C(O)(C_0-C_6alkyl), -C(O)O(C_0-C_6alkyl), -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -OH, C_1-C_6alkoxy, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino;

n is independently 0, 1, or 2; and

R_2 or R_3 may optionally be joined to R_4 by a bond to form a ring.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

A is CH.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_1 is a $-C_1-C_6$alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino or $-SO_n-(C_1-C_6$alkyl).

4. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_1 is a -cycloC_3-C_6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, or $-SO_n-(C_1-C_6$alkyl).

5. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_1 is a $-C_1-C_6$alkenyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, or $-SO_n-(C_1-C_6$alkyl).

6. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_1 is a heteroaryl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-

C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, or -SO_n-(C_1-C_6alkyl).

7. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_1 is a an –amino group, -C_1-C_6alkylamino group, or -(C_1-C_6alkyl)(C_1-C_6alkyl)amino group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC_3-C_6alkyl), -C(O)-O-(C_0-C_6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC_3-C_6alkyl, heterocycloC_3-C_6alkyl, aryl, heteroaryl, carbonyl, carbamoyl, -(C_0-C_6alkyl)(C_0-C_6alkyl)amino, or -SO_n-(C_1-C_6alkyl).

8. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_2 is an aryl, optionally substituted with 1-5 substituents; and

R_3 is a heteroaryl, optionally substituted with 1-5 substituents.

9. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_2 is an aryl, optionally substituted with 1-5 substituents; and

R_3 is an aryl, optionally substituted with 1-5 substituents.

10. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_2 is a carbonyl, optionally substituted with 1 substituent; and

R_3 is an aryl, optionally substituted with 1-5 substituents.

11. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_2 is a carbamoyl, optionally substituted with 1-2 substituents; and
R_3 is an aryl, optionally substituted with 1-5 substituents.

12. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein
R_2 and R_3 are each independently an aryl, optionally substituted, connected to each other by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system.

13. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein
R_2 is a -(C_1-C_6alkyl)-SO_n-(C_1-C_6alkyl), optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO_2, -COOH, carbonyl, -CN, -C_1-C_6alkyl, -SO_n-(C_1-C_6alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC_3-C_6alkyl, -NH-cycloC_3-C_6alkyl, -OH, or -(C_0-C_6alkyl)(C_0-C_6alkyl)amino substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C_1-C_6alkyl), -O(aryl), -COOH, -COO(C_1-C_6alkyl), halogen, -NO_2, -CN, or -C(O)-N(C_0-C_6alkyl)(C_0-C_6alkyl); and
R_3 is an aryl, optionally substituted with 1-5 substituents.

14. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein
R_2 is a -C(O)N-(C_0-C_6alkyl)(C_0-C_6alkyl), optionally substituted with 1-5 substituents; and
R_3 is an aryl, optionally substituted with 1-5 substituents.

15. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein
R_2 is –CN; and
R_3 is an aryl, optionally substituted with 1-5 substituents.

16. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

R_1 is $-C_1-C_6$alkyl, optionally substituted with 1-5 substituents;

R_2 and R_3 each independently is an aryl or heteroaryl, wherein each is optionally substituted with 1-5 substituents; and

R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system.

17. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

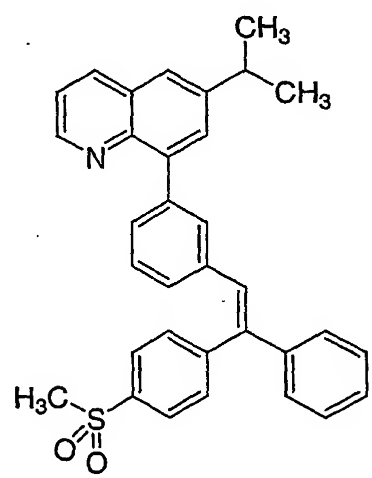
S_1, S_2, and S_3 are each H;

R_1 is $-C_1-C_6$alkyl, optionally substituted with 1-5 substituents;

R_2 and R_3 each independently is an aryl or heteroaryl, wherein each is optionally substituted with 1-5 substituents; and

R_2 and R_3 may be optionally connected by a thio, oxy, or (C_1-C_4alkyl) bridge to form a fused three ring system.

18. The compound according to claim 1, comprising



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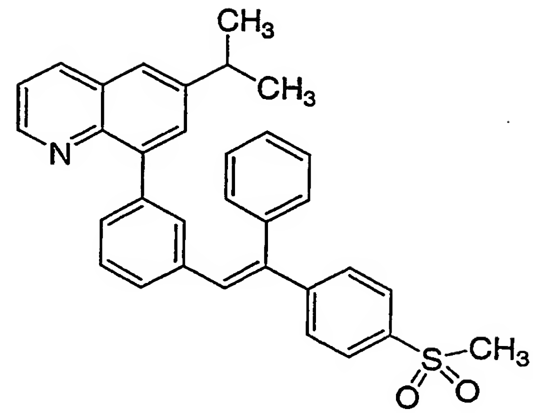
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CH3
N
S
CH3
O
O

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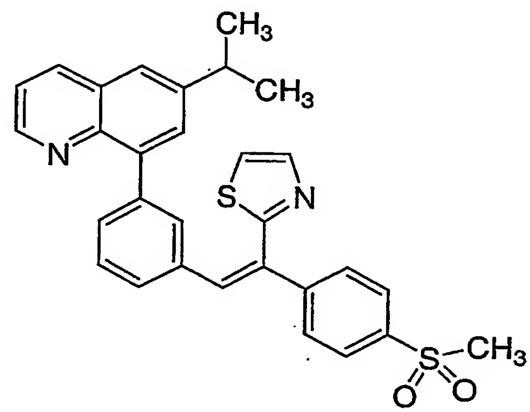
CH3
CH3
N
S
N
S
CH3
O
O

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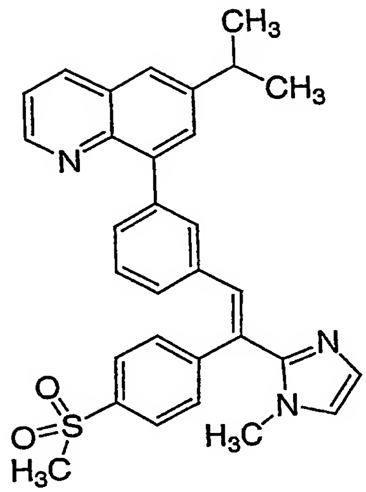
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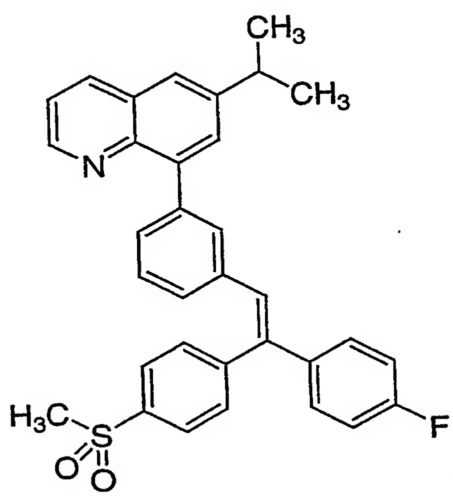
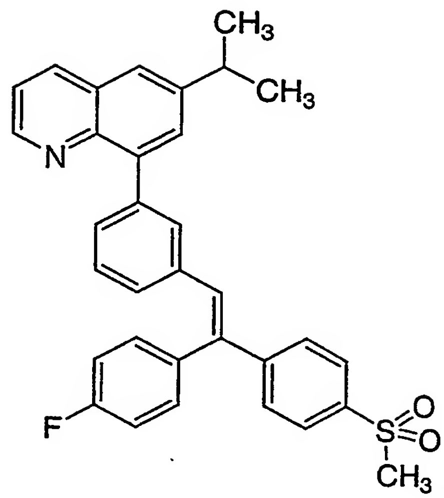
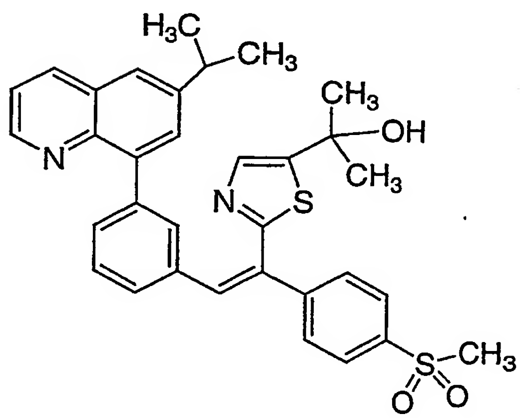
CH3
N
N
N
O
O=S
H3C
H3C

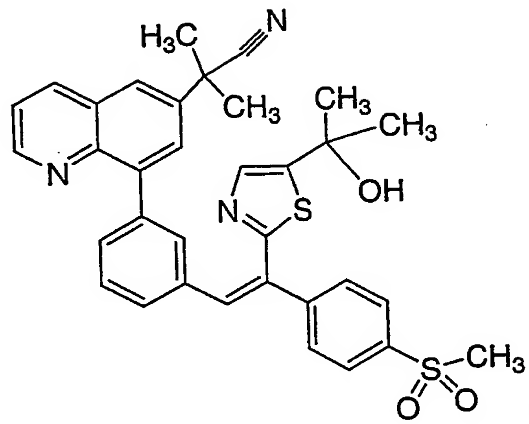
;


CH3
CH3
N
H3C
S
O
O
F

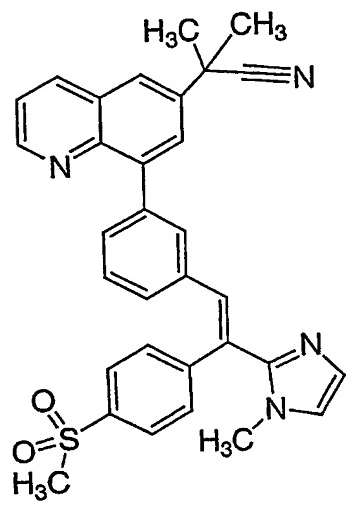
;


CH3
CH3
N
F
S
O
O
CH3
;

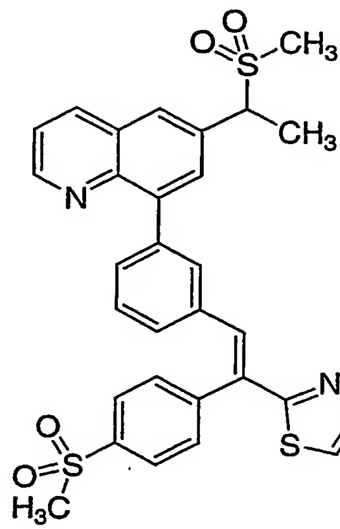

H3C
CH3
CH3
OH
CH3
N
N
S
S
CH3
O
O
;


H3C
N
CH3
CH3
CH3
N
OH
N
S
S
CH3
O
O

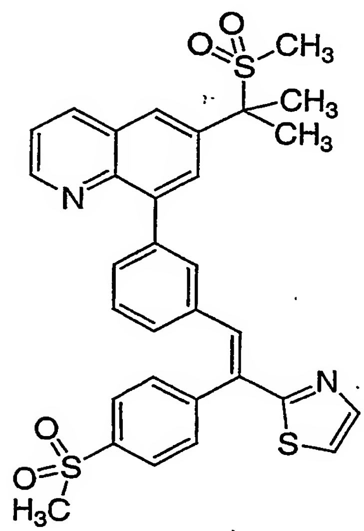
;


H3C
CH3
N
N
N
O
O
S
H3C
H3C
N

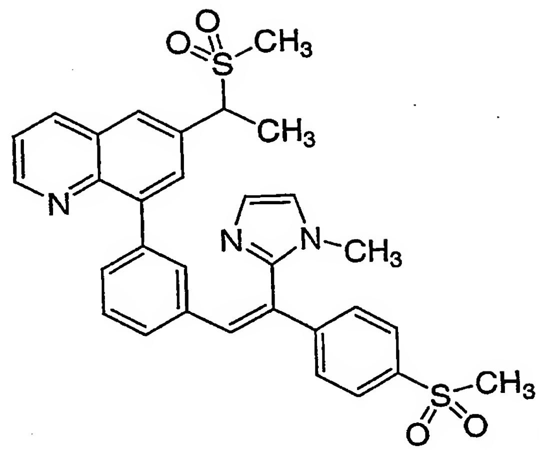
;


O
O=S
CH3
CH3
N
N
S
O
O=S
H3C

;

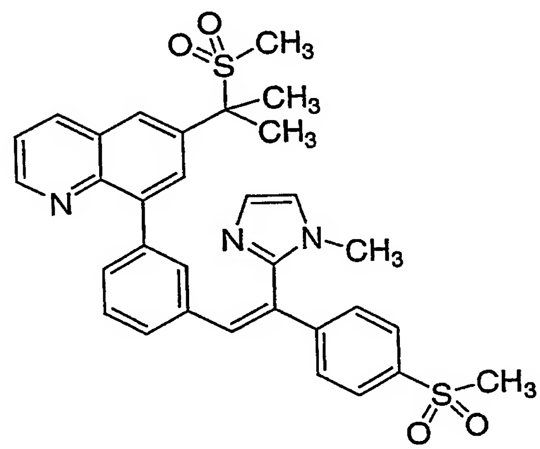

O
O=S
CH3
CH3
CH3
N
N
S
O
O=S
H3C

;



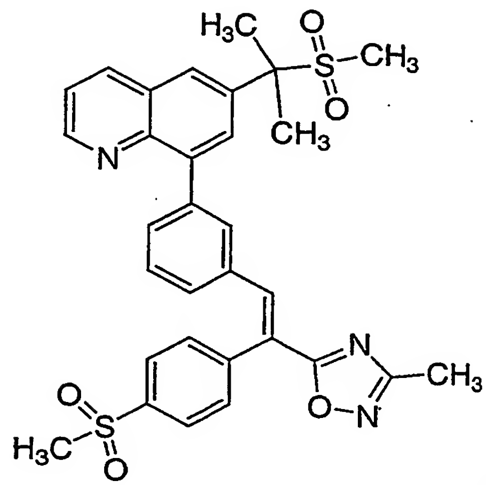
O
O=S-CH3
CH3
N
N
N-CH3
S-CH3
O O

;

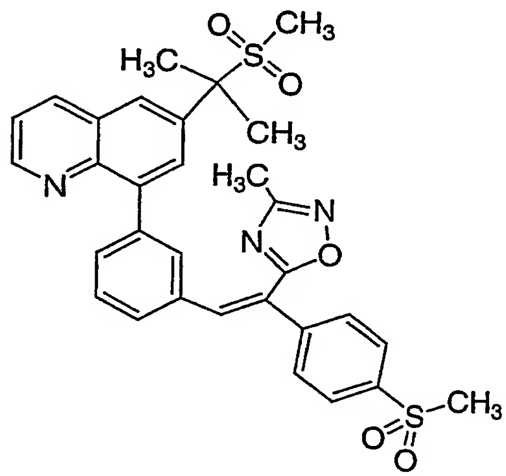


O
O=S-CH3
CH3
CH3
N
N
N-CH3
S-CH3
O O

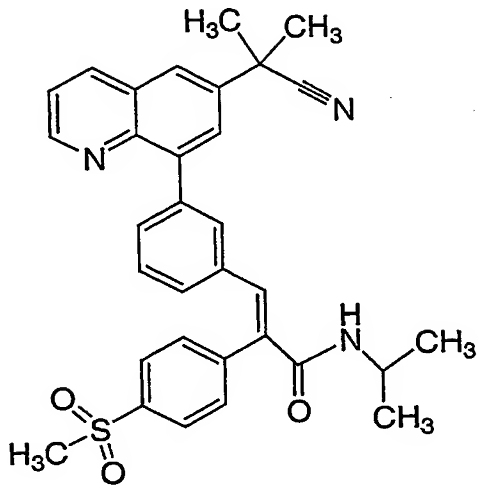
;


H3C
O
S
CH3
O
CH3
N
N
CH3
O
N
O
S
H3C
O

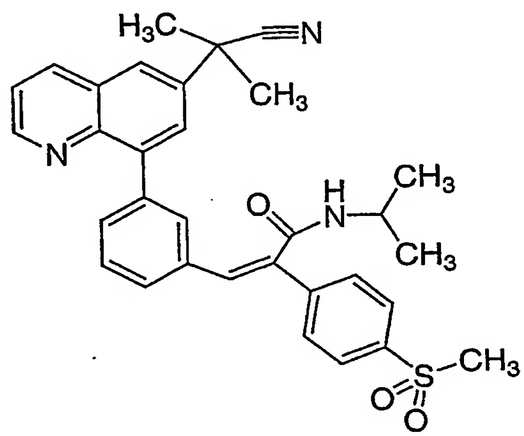
;


O
CH3
H3C
S
O
CH3
N
H3C
N
N
O
S
CH3
O
O

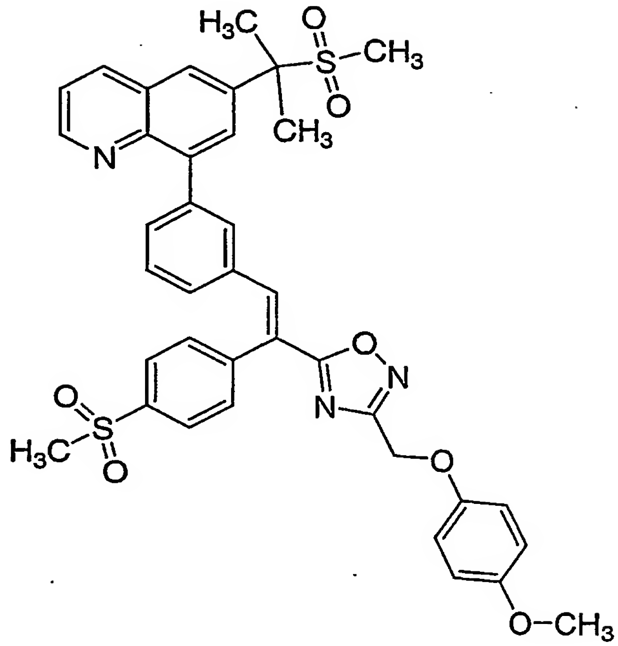
;


H3C
CH3
N
N
H
N
CH3
O
CH3
O
S
H3C
O

;

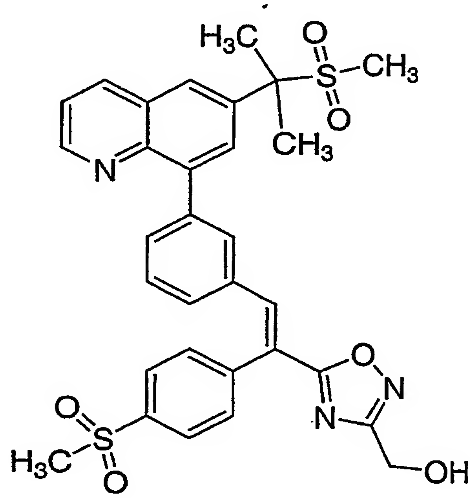

H3C
N
CH3
N
O
H
N
CH3
CH3
S
CH3
O
O

;



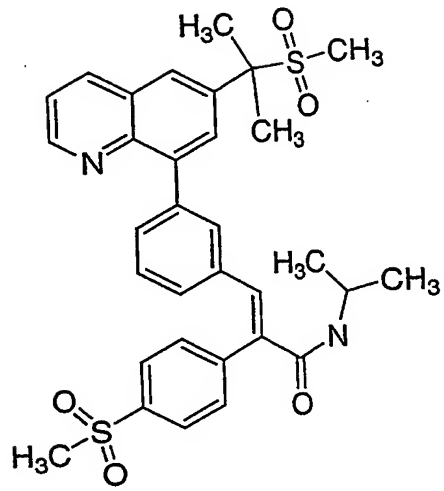
H3C
O
S
CH3
O
CH3
N
O
N
N
O
S
H3C
O
O
O-CH3

;



H3C
O
S
CH3
O
CH3
N
O
N
N
O
S
H3C
O
OH

;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S
CH3
O
CH3
N
H3C
CH3
N
O
O
S
H3C
O

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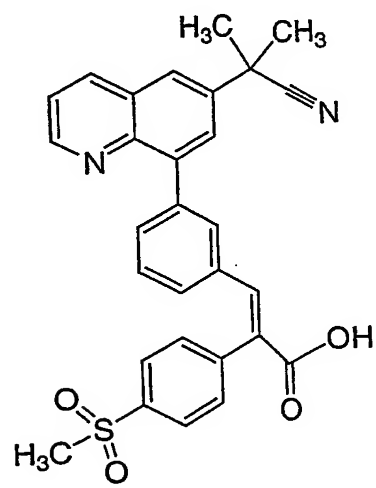
H3C
CH3
N
N
OH
O
O
S
H3C
O

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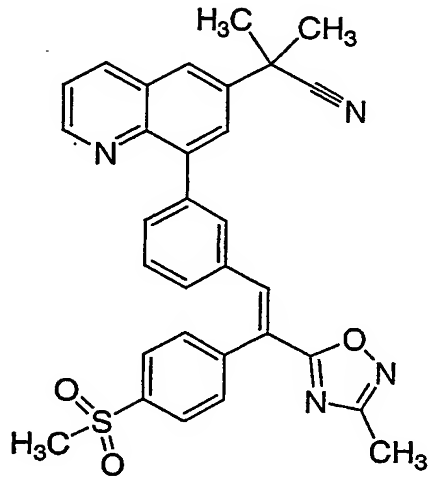

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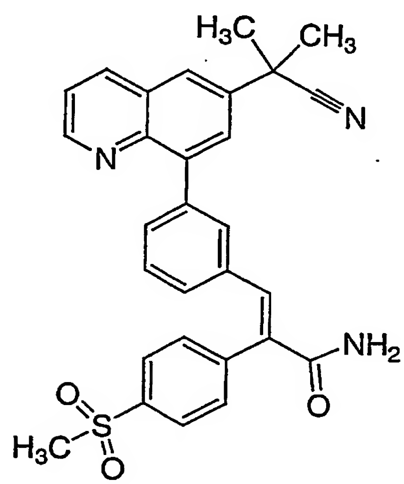

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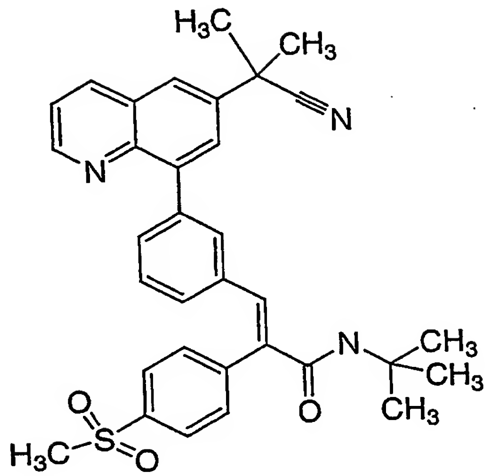
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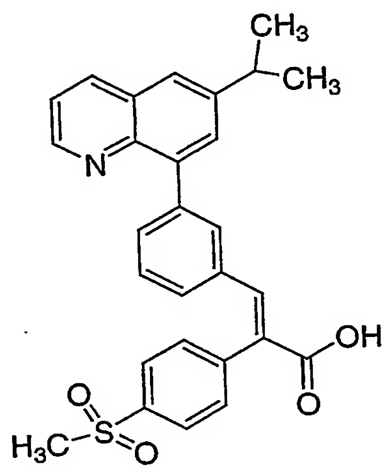
CH3
N
N
N
CH3
CH3
CH3
O
O
H3C-S=O

;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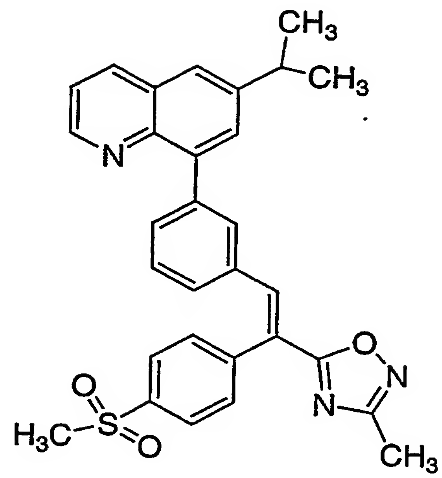
CH3
N
OH
O
O
H3C-S=O

;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N
O
N
N
CH3
O
H3C
S
O

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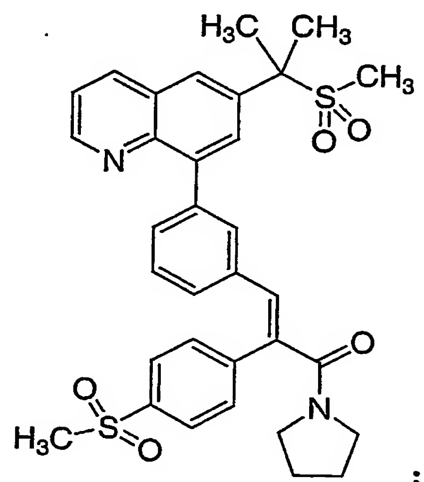
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CH3
S
CH3
O
O
N
O
O
H3C
S
O
N

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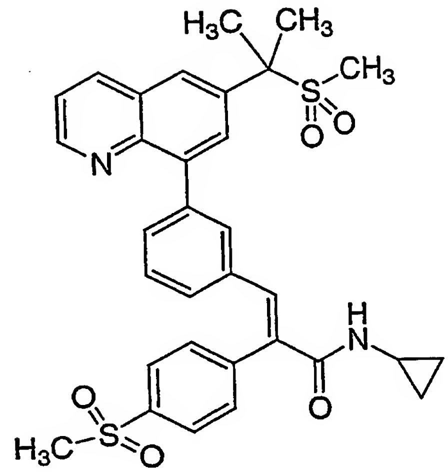
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CH3
CH3
S
O
O
N
H
N
O
O
S
H3C
O

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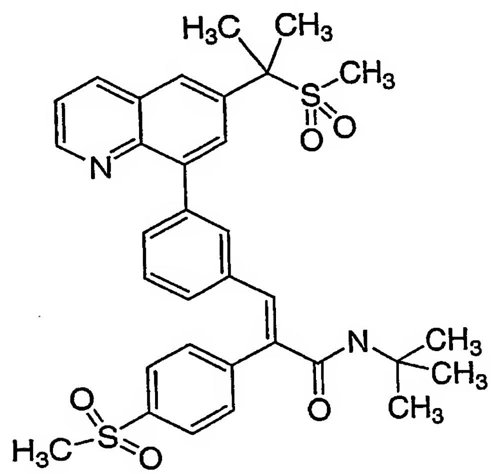
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CH3
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CH3
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S
H3C
O

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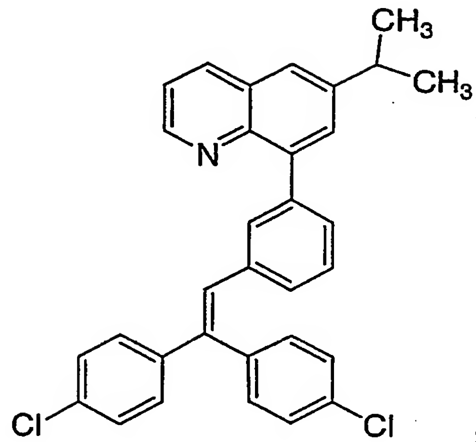

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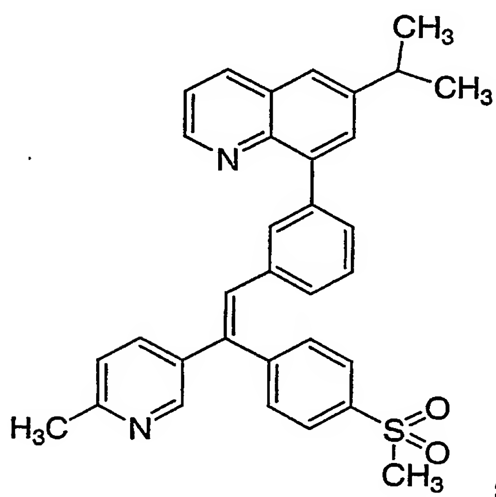

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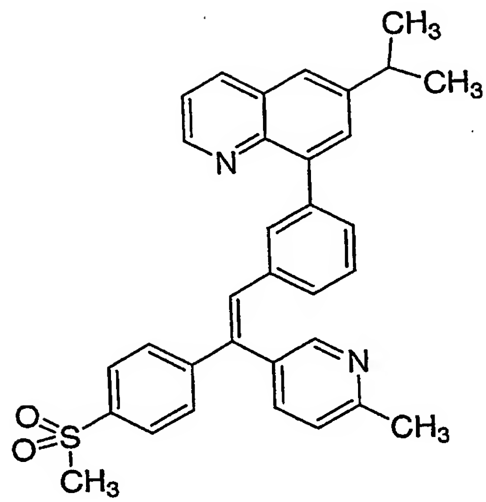
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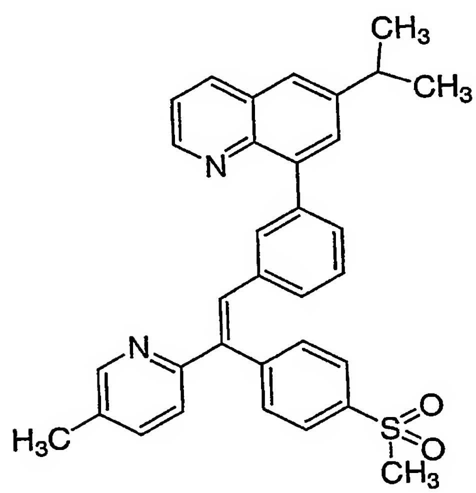
CH3
N
N
CH3
O
O
S
CH3
;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CH3
N
N
H3C
O
S
O
CH3
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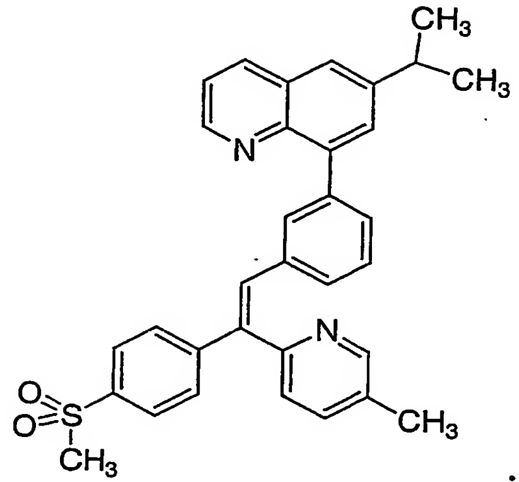
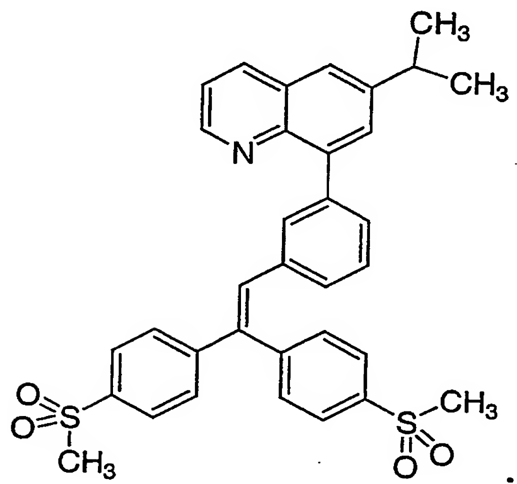

CH3
CH3
N
N
CH3
O
O
S
CH3

;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O
S
CH3
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CH3
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O

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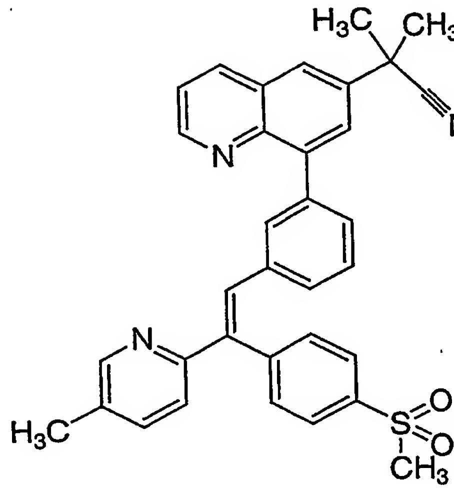
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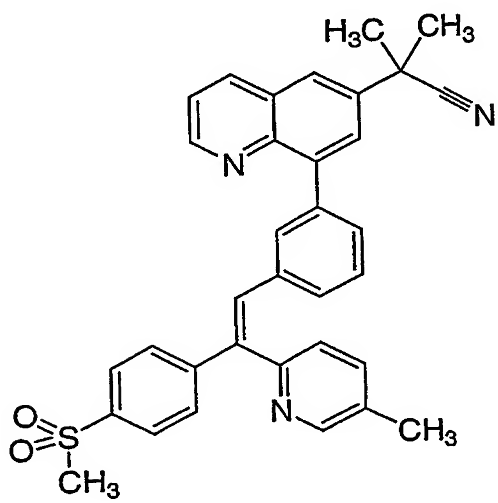
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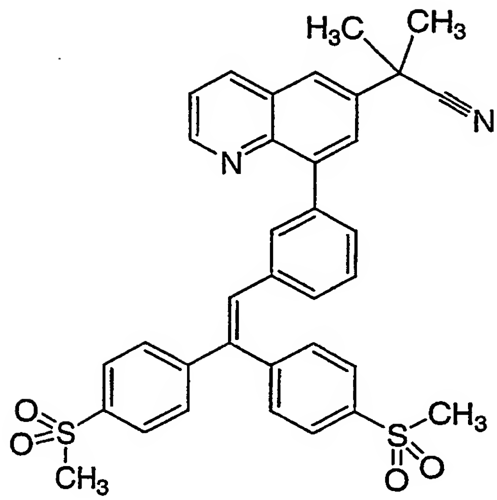

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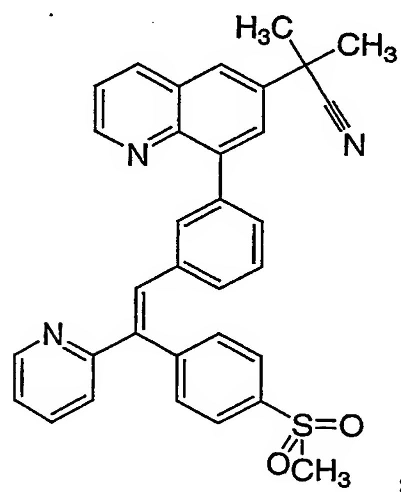

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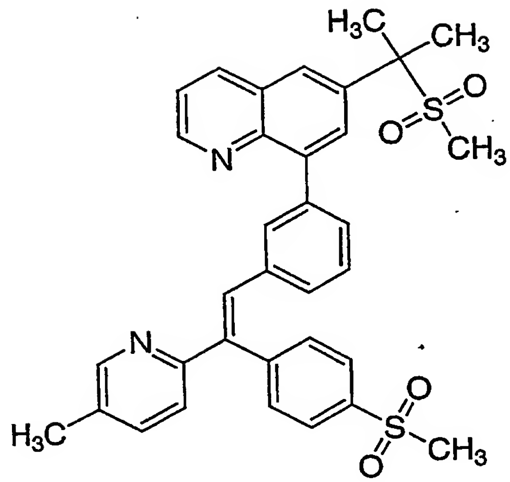
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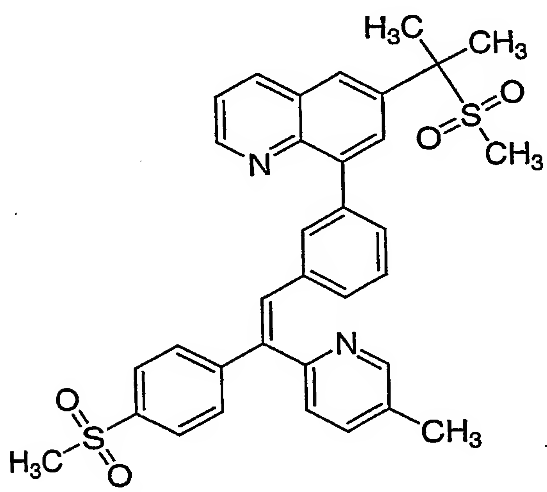
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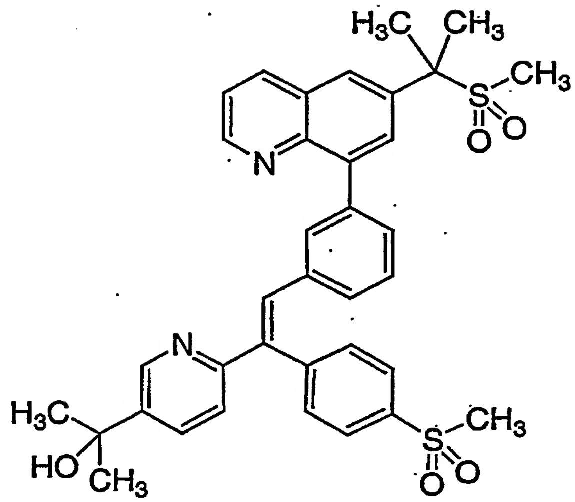
O

;



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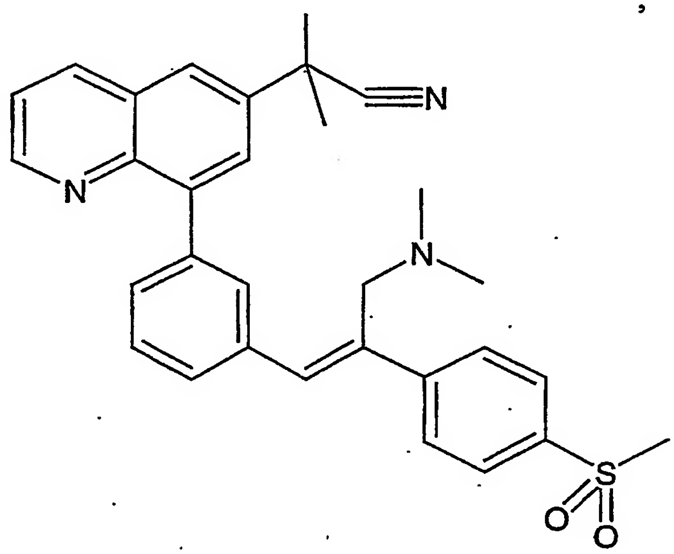


;

or a pharmaceutically acceptable salt thereof.

19. The compound according to claim 1, selected from 6-isopropyl-8-(3-{ (Z/E)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl}phenyl)quinoline;

6-isopropyl-8-{3-[(E/Z)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl } quinoline;
6-isopropyl-8-(3-{(E)-2-(l-methyl- lH-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline;
6-isopropyl-8-(3-{(Z/E)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline;
2-(2-{(E/Z)-2-[3-(6-isopropyl-8-quinolinyl)phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl}-1,3-thiazol-5-yl)-2-propanol;
2-[8-(3-{(E/Z)-2-[5-(1-hydroxy-l-methylethyl)-1,3-thiazol-2-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]-2-methylpropanenitrile;
2-methyl-2-[8-(3-{(E)-2-(1-methyl-1 H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]propanenitrile;
6-[1-(methylsulfonyl)ethyl]-8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline;
6-[1-methyl-l-(methylsulfonyl)ethyl]-8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline;
8-(3-{(Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-(methylsulfonyl)ethyl]quinoline;
8-(3-{(Z)-2-(1-methyl-lH-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-methyl-l-(methylsulfonyl)ethyl]quinoline;
6-[1-methyl-l-(methylsulfonyl)ethyl]-8-(3-{(E/Z)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline;
(E/Z)-3-{3-[6-(1-cyano-l-methylethyl)-8-quinolinyl]phenyl}-N-isopropyl-2-[4-(methylsulfonyl)phenyl]-2-propenamide;
8-(3-{(E)-2-{3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl}-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-methyl-l-(methylsulfonyl)ethyl] quinoline;
(5-{(E)-2-(3-{6-[1-methyl-l-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl}-1,2,4-oxadiazol-3-yl)methanol;
(E)-N-isopropyl-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl] -8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide;

(E)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid;
2-methyl-2-[8-(3-{(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl] propanenitrile;
(E)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenamide;
(E)-N-(tert-butyl)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenamide;
(E)-3-[3-(6-isopropyl-8-quinolinyl)phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid;
6-isopropyl-8-(3-{(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline;
(E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-2-propen-1-one;
(E)-N-cyclopropyl-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide;
(E)-N-(tert-butyl)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide;
8-{3-[2,2-bis(4-chlorophenyl)vinyl]phenyl}-6-isopropylquinoline;
6-isopropyl-8-(3-{(E/Z)-2-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline;
6-isopropyl-8-(3-{(E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline;
8-(3-{2,2-bis[4-(methylsulfonyl)phenyl]vinyl}phenyl)-6-isopropylquinoline;
2-methyl-2-[8-(3-{(E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]propanenitrile;
2-[8-(3-{2,2-bis[4-(methylsulfonyl)phenyl]vinyl}phenyl)-6-quinolinyl]-2-methylpropanenitrile;
2-methyl-2-(8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(2-pyridinyl)ethenyl]phenyl}-6-quinolinyl)propanenitrile;
6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-{(E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline;

2-(6-{(E)-2-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl}-3-pyridinyl)-2-propanol; or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising

a therapeutically effective amount of the compound of formula (I) according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier.

21. The pharmaceutical composition according to claim 20, further comprising a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, an M2/M3 antagonist, a corticosteroid, an Hl receptor antagonist or a beta 2 adrenoceptor agonist.

22. The pharmaceutical composition according to claim 20, further comprising a COX-2 selective inhibitor, a statin, or an NSAID.

23. A method of treatment or prevention of asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral

induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

24. A precursor compound which forms in vivo the compound of formula (I) according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof.

25. A method of treatment or prevention of asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues comprising the step of forming in vivo a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1.

26. A compound of formula (I), according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof for use as phosphodiesterase inhibitors.

27. Use of a compound of formula (I), according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment or prevention of asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusiori injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

28. A phosphodiesterase-4 inhibitor pharmaceutical composition comprising an acceptable phosphodiesterase-4-inhibiting amount of a compound of formula (I), as defined in any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

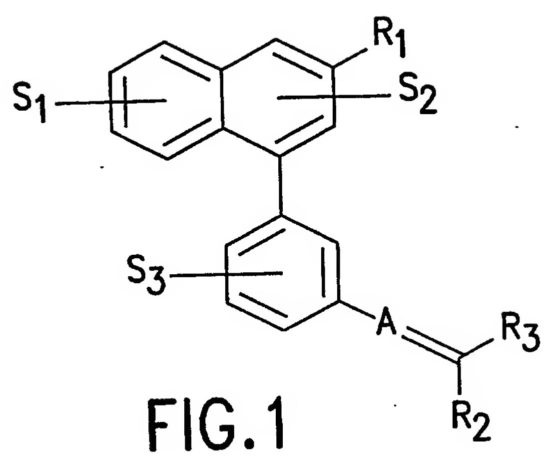


FIG.1

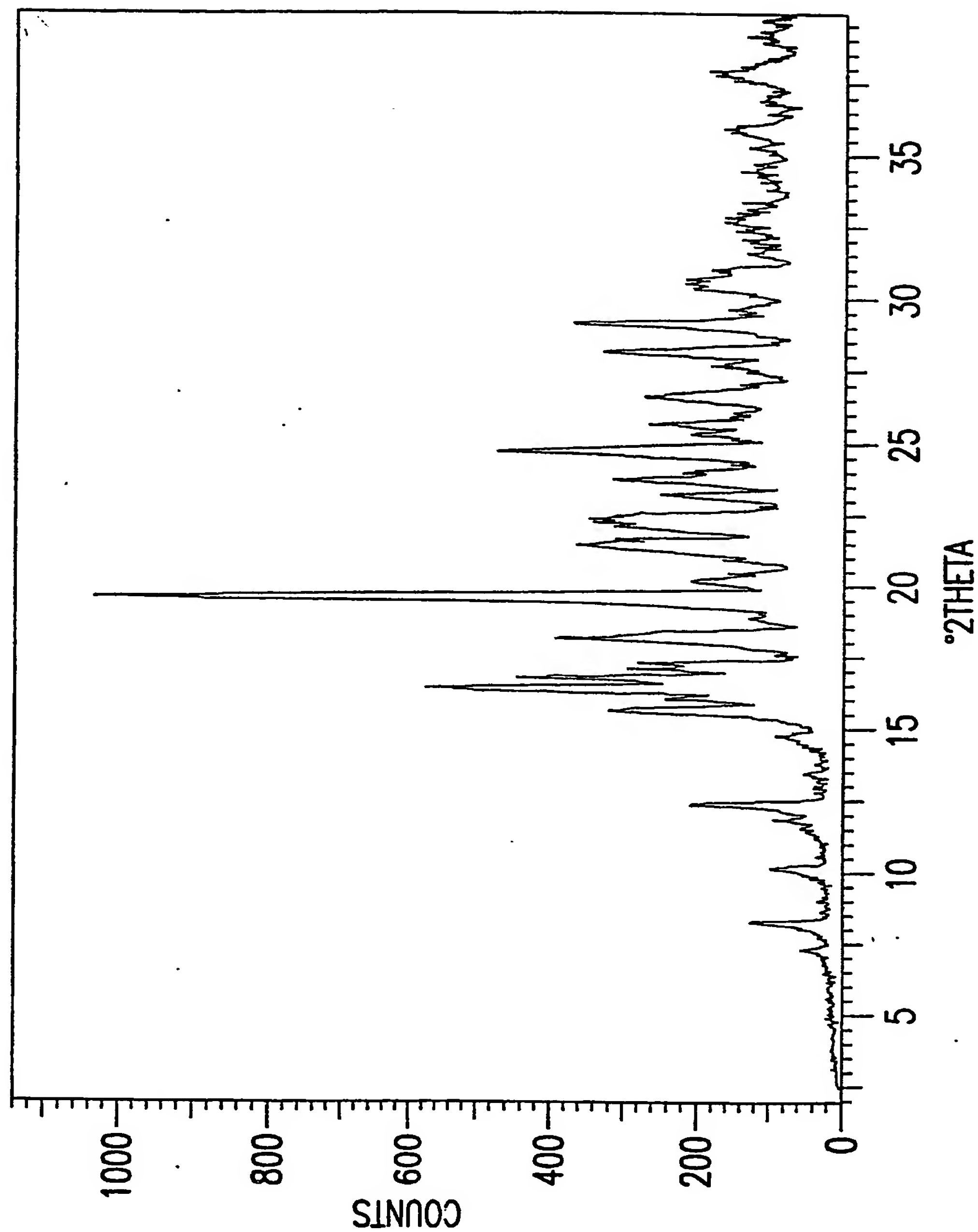


FIG.2

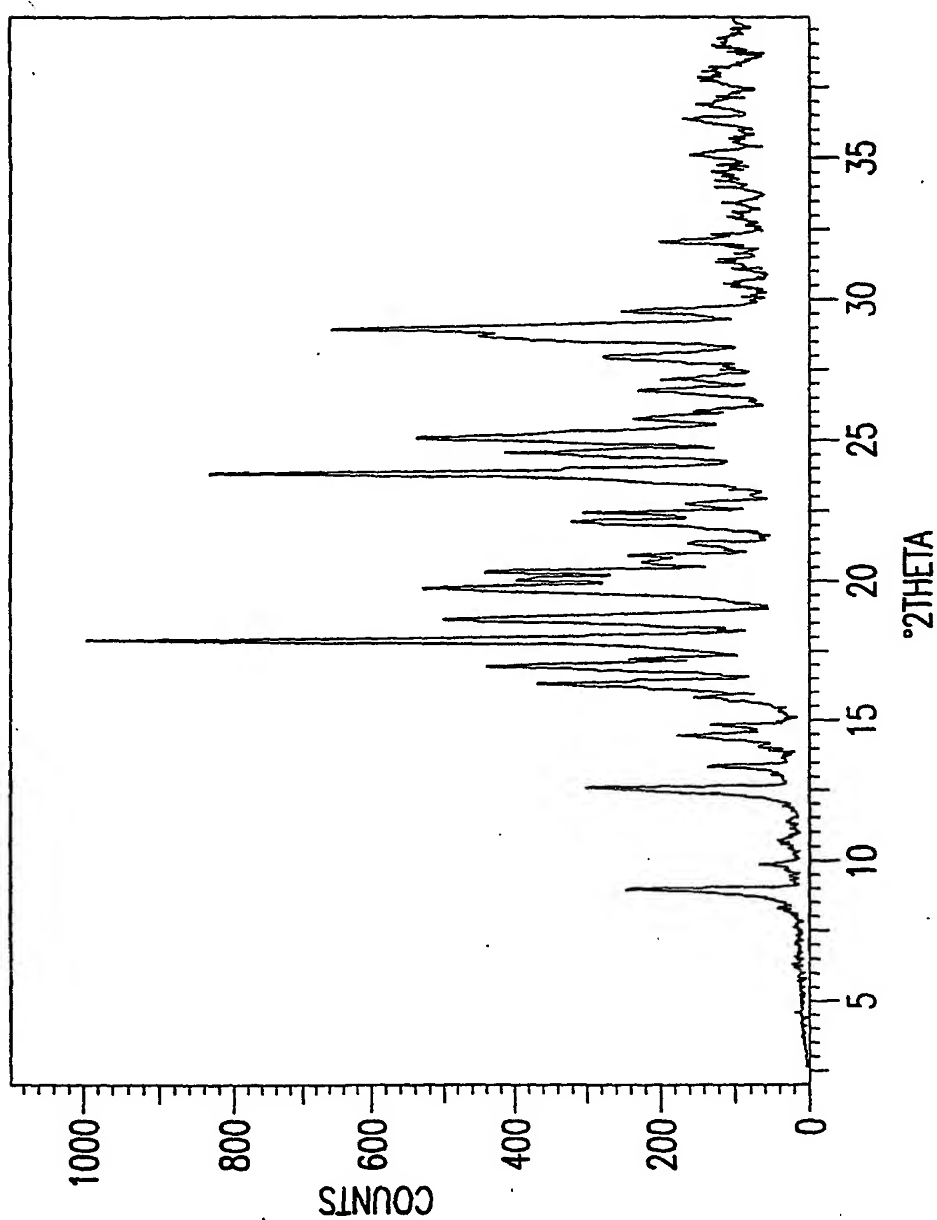


FIG.3

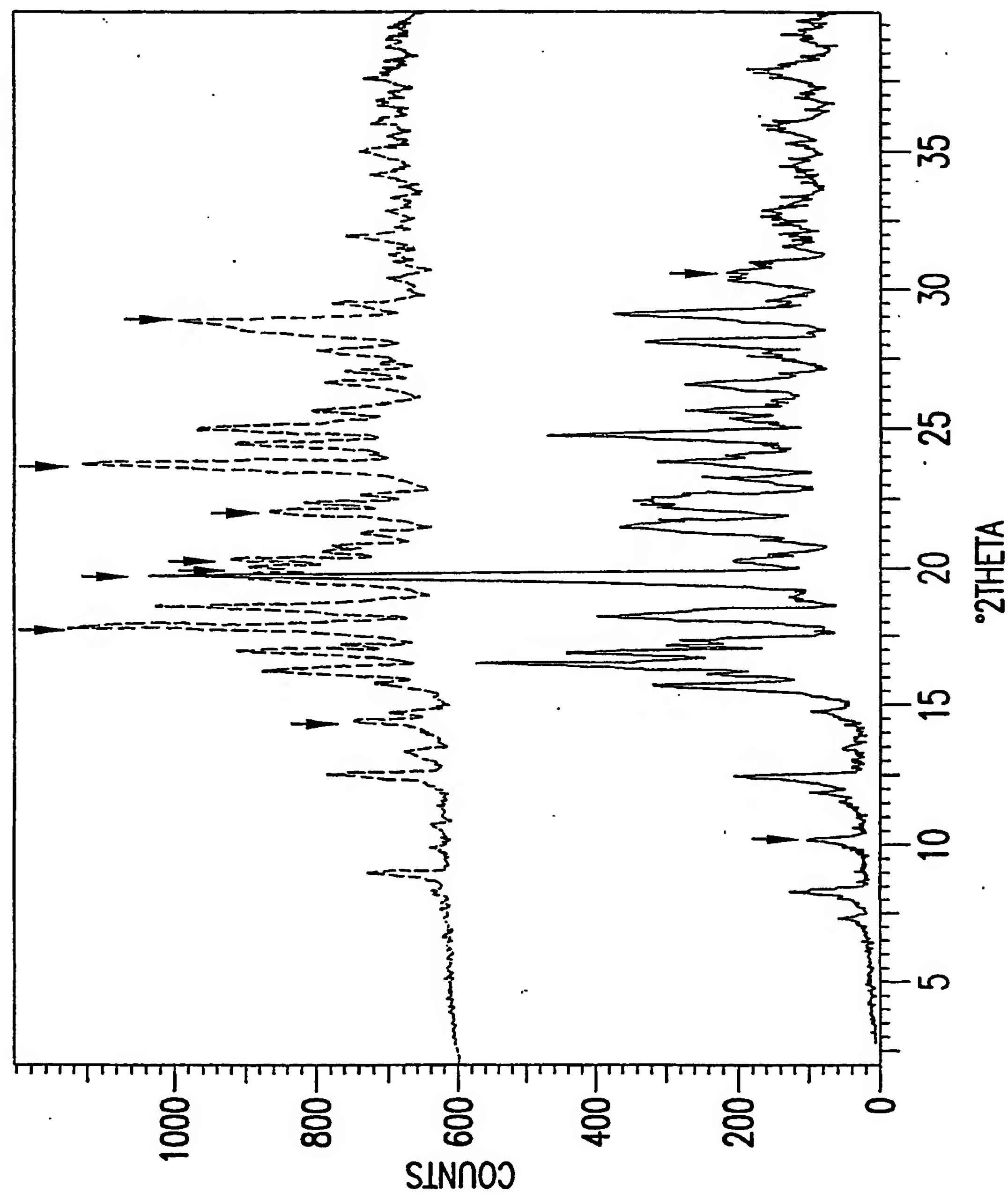


FIG.4

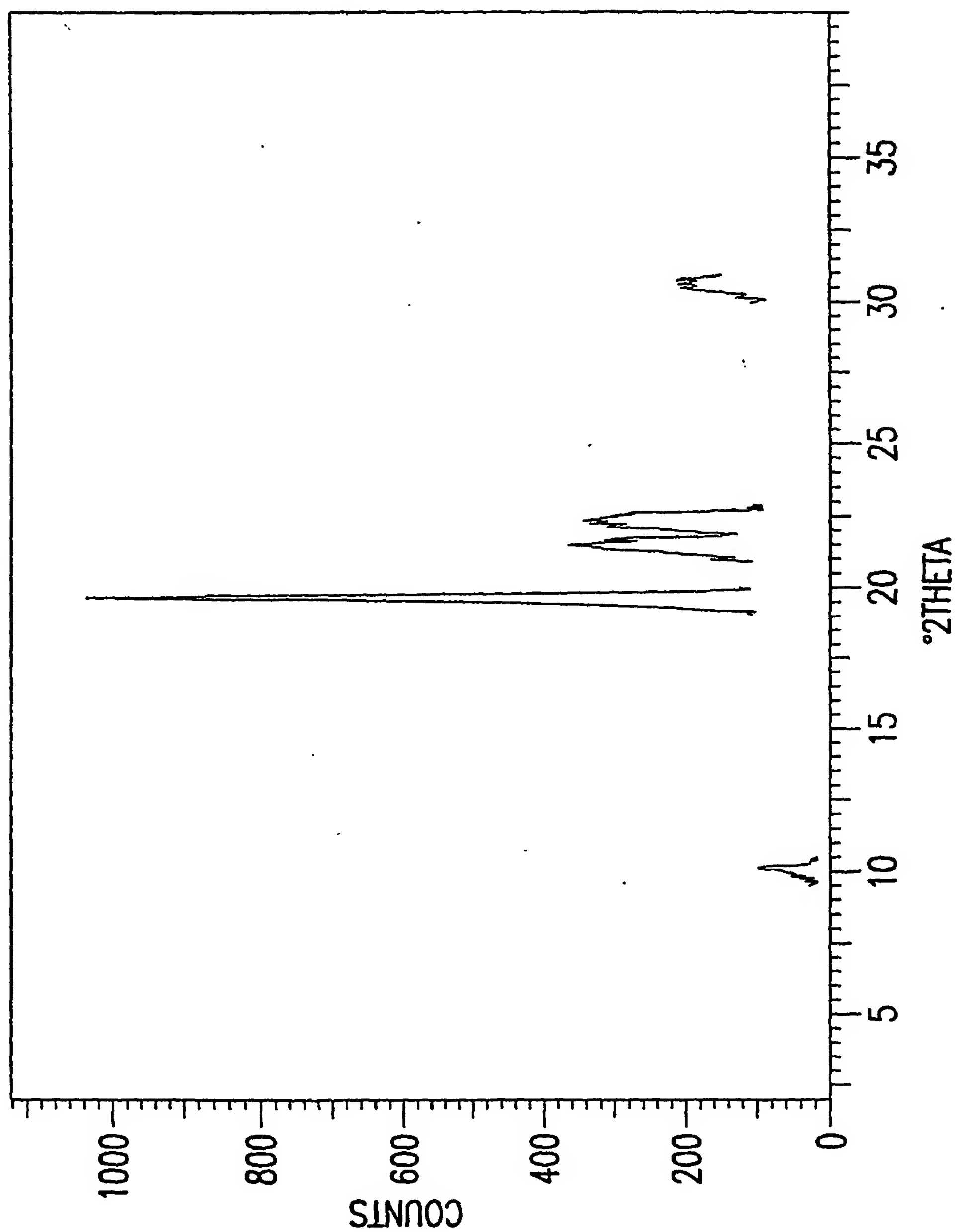


FIG.5

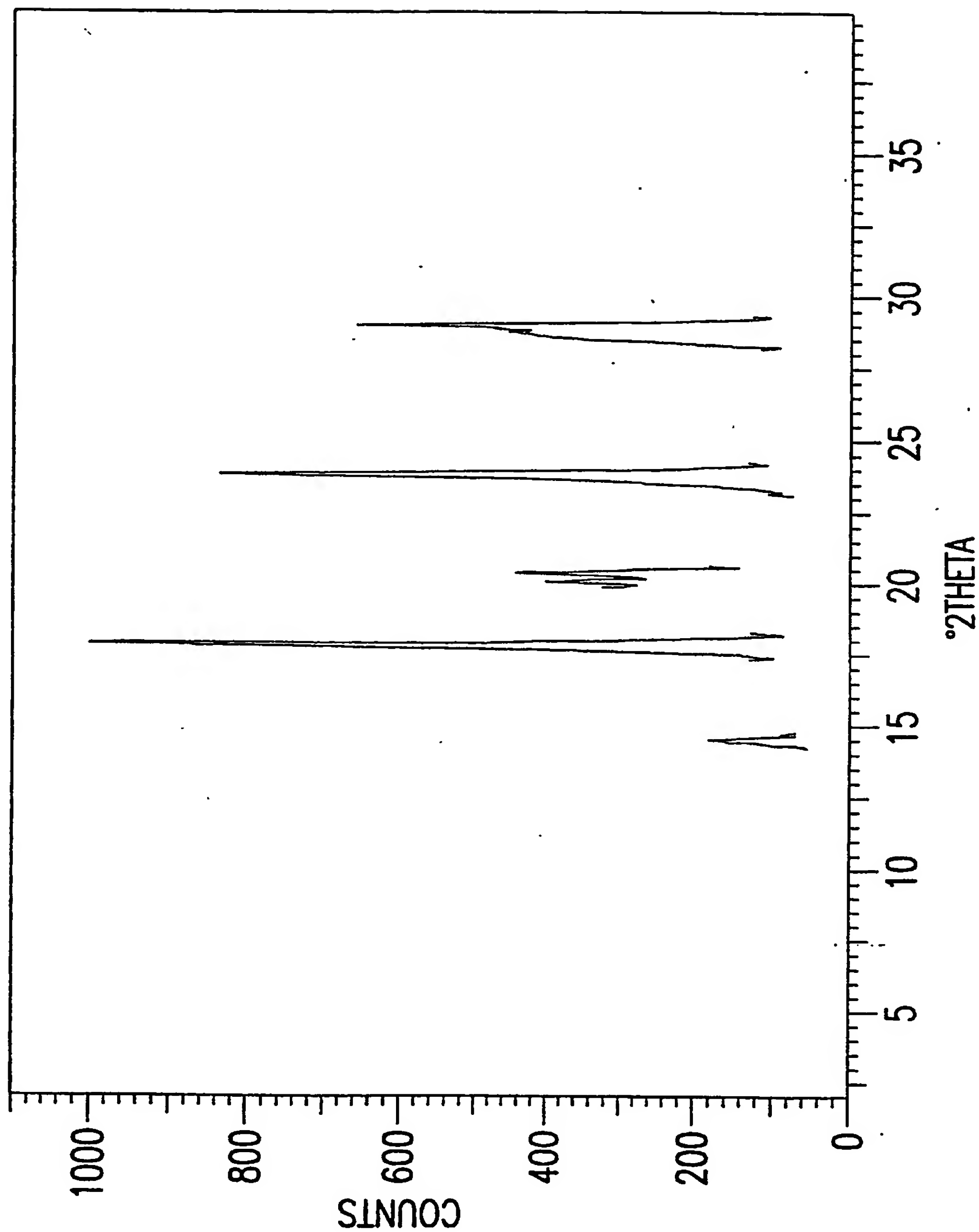


FIG.6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01559

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/12 A61K31/47 A61K31/4709 C07D215/14 C07D401/10 C07D413/10 C07D417/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 35283 A (CELLTECH THERAPEUTICS LTD) 28 December 1995 (1995-12-28) page 68 -page 70; claim 1	1,2,7, 12,16, 17,20, 23,25-28
Y	WO 94 22852 A (SYNTEX INC) 13 October 1994 (1994-10-13) cited in the application page 60; claim 1 page 22, line 18 - line 33	1-23, 25-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2001	03.05.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP 1 052 254 A (EISAI CO LTD) 15 November 2000 (2000-11-15) page 74 -page 76; claim 1 page 3, line 5 - line 9 page 67; example 69	1-23, 25-28
Y	& WO 99 37622 A (EISAI CO., LTD.) 29 July 1999 (1999-07-29) ---	1-23, 25-28
A	US 5 580 888 A (WARRELLOW GRAHAM J ET AL) 3 December 1996 (1996-12-03) cited in the application the whole document -----	1-23, 25-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/01559

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23 and 25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 24
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 24

Present claim 24 relates to compounds defined by reference to a desirable characteristic or property, namely to "...precursor compound(s)..." (i.e., prodrugs) "...which form in vivo the compound(s) of formula (I)..."
This claim thus covers all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT).
An attempt is made to define the respective compounds by reference to a result to be achieved.
The term "precursor compound(s)" does not comprise any information as regards the structure of the compounds concerned. It is therefore impossible to compare the compounds of the present claim 24 with what is set out in the prior art.
Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of the present claim 1.
The compounds of the present claim 24 have not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

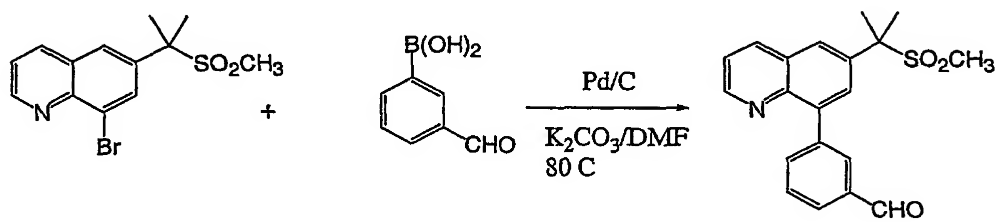
Intern   l Application No
PCT/CA 00/01559

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9535283 A	28-12-1995	AU 707717 B	15-07-1999
		AU 2746395 A	15-01-1996
		CA 2192645 A	28-12-1995
		EP 0766669 A	09-04-1997
		JP 10503174 T	24-03-1998
WO 9422852 A	13-10-1994	US 5455252 A	03-10-1995
		AT 170855 T	15-09-1998
		AU 679222 B	26-06-1997
		AU 6412994 A	24-10-1994
		CA 2159603 A	13-10-1994
		DE 69413215 D	15-10-1998
		DE 69413215 T	28-01-1999
		DK 691966 T	08-02-1999
		EP 0691966 A	17-01-1996
		ES 2120028 T	16-10-1998
		FI 954651 A	29-09-1995
		HU 9500111 A	28-06-1995
		HU 73181 A	28-06-1996
		JP 8511238 T	26-11-1996
		NO 953879 A	22-11-1995
		NZ 263436 A	22-08-1997
EP 1052254 A	15-11-2000	JP 11209350 A	03-08-1999
		WO 9937622 A	29-07-1999
US 5580888 A	03-12-1996	AT 177097 T	15-03-1999
		AU 678797 B	12-06-1997
		AU 5709394 A	19-07-1994
		CA 2129040 A	07-07-1994
		DE 69323732 D	08-04-1999
		DE 69323732 T	09-09-1999
		EP 0626957 A	07-12-1994
		ES 2131668 T	01-08-1999
		WO 9414800 A	07-07-1994
		JP 7504687 T	25-05-1995

A solution of the sulfone (product from the previous step, 1 equiv) in DMF was cooled to about –10 to 0°C. Sodium t-butoxide (~1 equiv) was added . A solution of methyl iodide/DMF solution (~1 equiv of MeI) was added slowly while maintaining temperature at about –10 to 0°C.

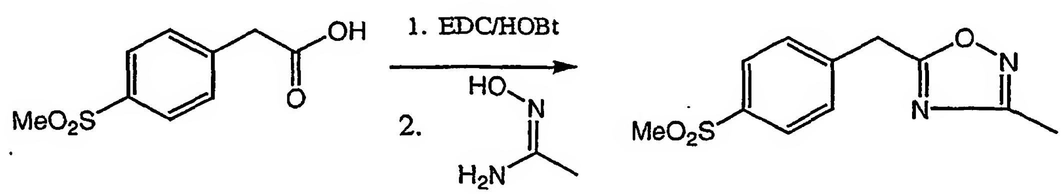
A second portion of solid sodium t-butoxide (~1 equiv) was added, followed by methyl iodide/DMF solution (~1 equiv) was added while maintaining the temperature at –5 to 10 °C (Additional base and MeI may be added if the reaction was not completed). The reaction was quenched by adition of water and the product crystallized, which was isolated and dried.

Step 5. Suzuki Coupling



To a solution of the sulfone from the previous step (1 equiv) was added Pd/C (5 or 10 w%, 0.005-0.1 equiv), potassium carbonate (2-3 equiv), and 3-formyl phenylboronic acid (1-2 equiv). The degassed reaction mixture was heated at 60-120°C until the reaction was complete. The mixture was filtered and the filtrate was diluted with water. The product crystallized and was isolated by filtration and dried.

Step 6. Oxadiazole

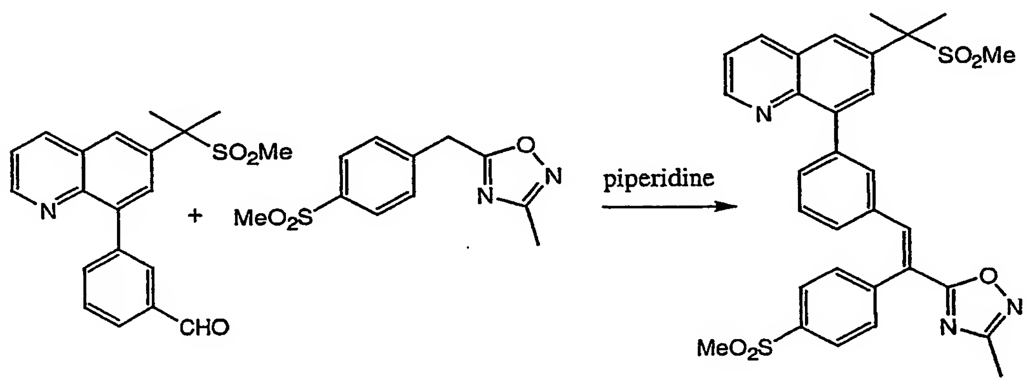


To the mixture of hydroxy benzotriazole ("HOBt") hydrate (1-1.5 equiv), 4-methylsulfonylphenylacetic acid (1 equiv) in acetonitrile was added EDC hydrochloride (1-1.5 equiv). The slurry was aged at about 20-30°C for 30min.

Other N-OH compounds, such as N-hydroxyphthalimide, 2-hydroxypyridine N-oxide, N-hydroxysuccinimide, can also be used to replace HOBt. Other carbodiimides, such as dicyclohexylcarbodiimide and diisopropylcarbodiimide can be used to replace EDC hydrochloride (ethyl dimethylaminopropylcarbodiimide hydrochloride).

To the slurry was added acetamide oxime (1-1.5 equiv). The resulting mixture was then heated at reflux until the reaction was complete. The resulting solution was concentrated and diluted with ethyl acetate. To the resulting mixture was washed with aqueous sodium bicarbonate. The solution was solvent switched to 2-propanol and product crystallized upon cooling, which was isolated and dried.

Step 7. Condensation to form Example 14



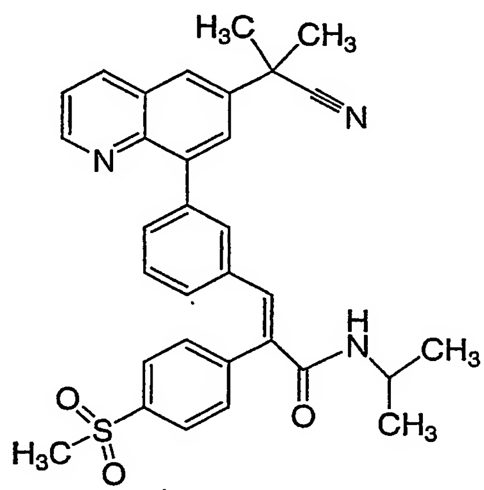
To a slurry of the aldehyde from step 5 above (1 equiv) in 2-propanol was added the oxadiazole from step 6 above (1-1.5 equiv), followed by piperidine (0.2-1.5 equiv).

In place of 2-propanol, other solvents such as, for example, DMF, acetonitrile, 1-propanol, toluene, esters, and other alcohols. Piperidine serves as a basic initiator. In place of piperidine, other amine bases, especially secondary amines, can be used.

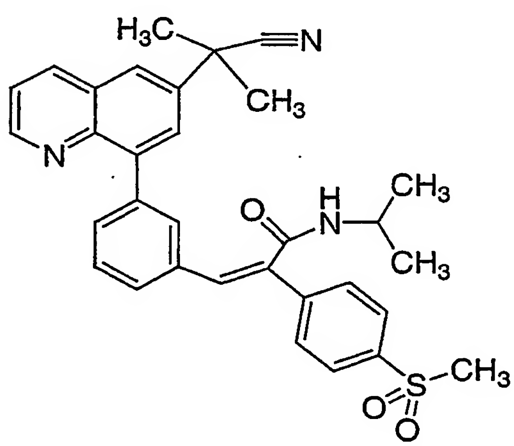
The resulting mixture was heated at reflux over molecular sieves until reaction completed. After cooling, the product was isolated by filtration and dried.

EXAMPLES 16 and 17

(E/Z)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-N-isopropyl-2-[4-(methylsulfonyl)phenyl]-2-propenamide



Example 16



Example 17

Examples 16 and 17 were prepared following the procedure described previously for Examples 14 and 15 but substituting the aryl bromide **AB2** for **AB5** and the bromoquinoline **Q5** for **Q3** as the starting materials. Examples 16 and 17 were obtained as a 4:1 mixture.

NMR ^{1}H (500 MHz, Acetone-d_6) Major(E) isomer (Example 16): ∂ 8.89 (dd, 1H), 8.43 (dd, 1H), 8.09 (d, 1H), 7.90 (d, 2H), 7.81 (d, 1H), 7.68 (s, 1H), 7.57 (m, 4 H), 7.45 (s, 1H), 7.29 (t, 1H), 7.04 (d, 1 H), 6.71 (bd, 1H), 4.13 (m, 1H) 2.92 (s, 3H), 1.87 (s, 6H), 1.12 (d, 6H).

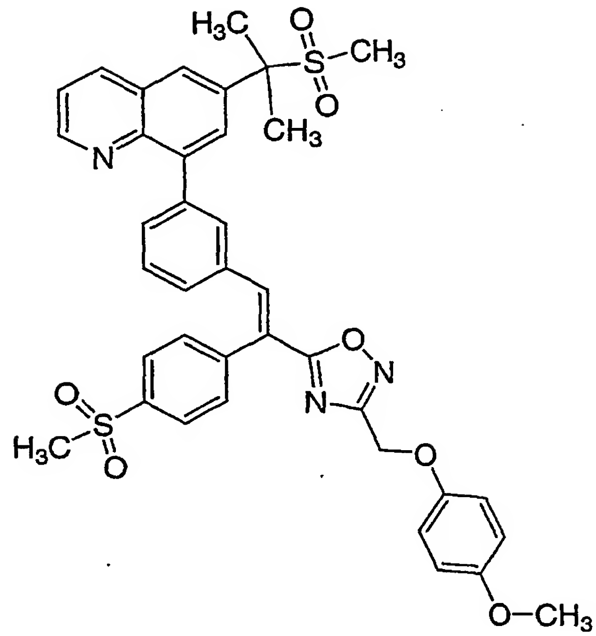
MS (M+1): 538.3

Minor(Z) isomer (Example 17): ∂ 8.93 (dd, 1H), 8.48 (dd, 1H), 8.14 (d, 1H), 7.94 (m, 4H), 7.85 (d, 2H), 7.70 (dd, 2H), 7.59 (q, 1H), 7.50 (m, 2 H), 7.28 (s, 1H), 4.15 (m, 1H) 3.13 (s, 3H), 1.91 (s, 6H), 1.04 (d, 6H).

MS (M+1): 538.3

EXAMPLE 18

8-(3-{(E)-2-{3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl}-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline



Example 18 was prepared by the following procedure.

Step 1 (Scheme 3): (4-methoxyphenoxy)acetonitrile

A mixture of 4-methoxyphenol (10g, 80mmol), chloroacetonitrile (7.0mL, 111mmol) and K_2CO_3 (26g, 188mmol) in acetone (150 mL) was stirred at r.t. for 18h. The mixture was filtered, concentrated and purified by flash chromatography (Hex:EtOAc, 4:1) to yield (4-methoxyphenoxy)acetonitrile as a clear oil.

Step 2 (Scheme 3): (4-methoxyphenoxy)acetamide oxime

A mixture of the (4-methoxyphenoxy)acetonitrile product (5.0g, 31mmol) from step 1, hydroxylamine hydrochloride (4.3g, 62mmol) and sodium acetate (5.1g, 62mmol) in MeOH (100mL) was stirred at r.t. for 2h. The resulting mixture was filtered on Celite®, concentrated, stirred in $CHCl_3$ for 18h and filtered. The resulting solution was concentrated to yield (4-methoxyphenoxy)acetamide oxime as a gum.

Step 3 (Scheme 3, Oxadiazole **OX2**): 3-[(4-methoxyphenoxy)methyl]-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole

3-[(4-methoxyphenoxy)methyl]-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole was prepared following the procedure as described in Scheme 3 for **AB5** step 1 (**OX1**) but substituting the (4-methoxyphenoxy)acetamide oxime from step 2 above for acetamide oxime and heating the reaction at 90°C for 6h. Purification by flash chromatography (Hex:EtOAc, 3:2 to 1:4) yielded the desired material as a pale brown solid.

Step 4: 3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}benzaldehyde

To bromoquinoline **Q3** (10.1g, 30.9mmol) 3-formylbenzeneboronic acid (5.8g, 38.7mmol), tetrakis(triphenylphosphine)-palladium (0) (2.1g 1.86mmol) and sodium carbonate (39mL, 2M) was added DME (330mL). After degassing, the mixture was heated at 80°C overnight. After cooling to r.t. the resulting mixture was quenched with H_2O, and extracted with EtOAc. The organic extracts were washed (H_2O, brine), dried ($MgSO_4$), filtered and concentrated. Stirring in ether, followed by isolation by filtration gave 3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}benzaldehyde.

Step 5: 8-(3-{(E)-2-{3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl}-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline

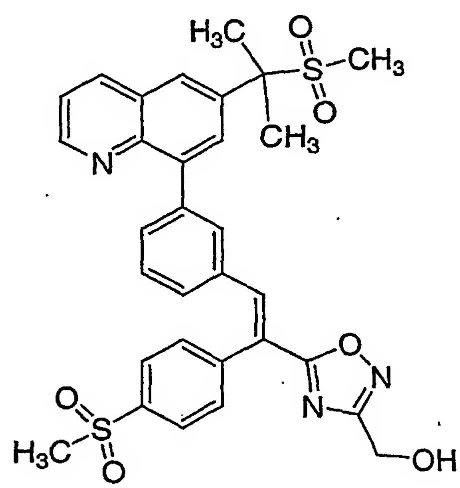
A mixture of the product from present step 4 (150mg, 0.42mmol), the oxadiazole **OX2** from present step 3 above (175mg, 0.47mmol) and piperidine (0.1mL, 1.0mmol) in toluene (0.6mL) was heated at 120°C for 3h. The mixture was purified by flash chromatography (Hex:EtOAc, 3:2 to 1:4) to yield Example 18 as a foam.

NMR ^{1}H (400MHz, Acetone-d_6) ∂ 8.90 (q, 1H), 8.42 (q, 1H), 8.24 (d, 1H), 8.20 (s, 1H), 8.02 (m, 3H), 7.75-7.66 (m, 4H), 7.55 (q, 1H), 7.39 (t, 1H), 7.25 (d,

1H), 7.00 (d, 2H), 6.87 (d, 2H), 5.17 (s, 2H), 3.73 (s, 3H), 3.03 (s, 3H), 2.80 (s, 3H), 1.96 (s, 6H).

EXAMPLE 19

(5-{(E)-2-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl}-1,2,4-oxadiazol-3-yl)methanol

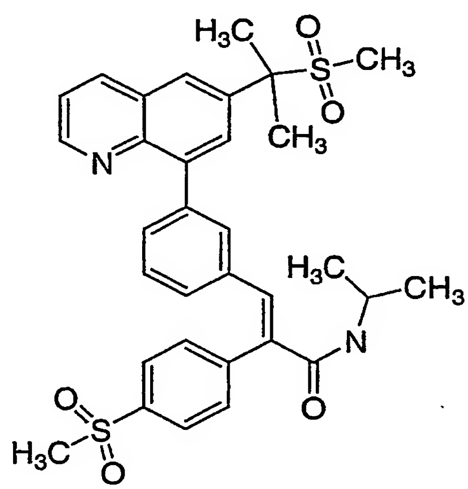


Example 19 was prepared by the following procedure. To a solution of the Example 18 compound (250mg, 0.35mmol) in acetonitrile:water (4:1, 8 mL) was added CAN (330mg, 0.62mmol) in two portions at r.t. After 3h at r.t., the mixture was diluted with saturated $NaHCO_3$ solution, diluted with water and extracted with EtOAc. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 3:7) yielded (5-{(E)-2-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl}-1,2,4-oxadiazol-3-yl)methanol as a pale yellow foam.

NMR ^{1}H (400MHz, Acetone-d_6) ∂ 8.90 (q, 1H), 8.42 (q, 1H), 8.25 (d, 1H), 8.15 (s, 1H), 8.02 (m, 3H), 7.73-7.65 (m, 4H), 7.55 (q, 1H), 7.38 (t, 1H), 7.23 (d, 1H), 4.67 (m, 3H), 3.04 (s, 3H), 2.82 (s, 3H), 1.96 (s, 6H).

EXAMPLE 20

(E)-N-isopropyl-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide



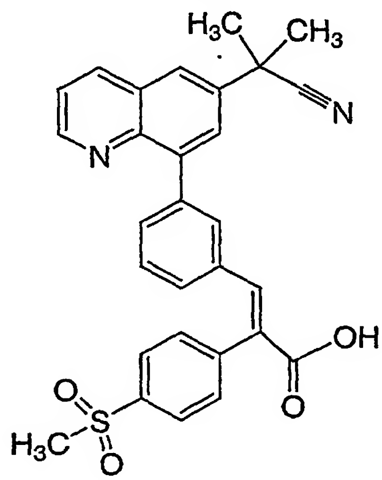
Example 20 was prepared by following the procedure described above for Examples 14 and 15 but substituting the aryl bromide **AB2** for **AB5**, and using the bromoquinoline **Q3**, as the starting materials.

NMR ^{1}H (300MHz, Acetone-d_6) ∂ 8.89 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.99 (d, 1H), 7.88 (d, 2H), 7.67 (s, 1H), 7.53 (m, 4H), 7.43 (s, 1H), 7.28 (t, 1H), 7.05 (d, 1H), 6.71 (bd, 1H), 4.14 (m, 1H) 2.9 (s, 3H), 1.95 (s, 6H), 1.13 (d, 6H).

MS(M+1): 591.3

EXAMPLE 21

(E)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid



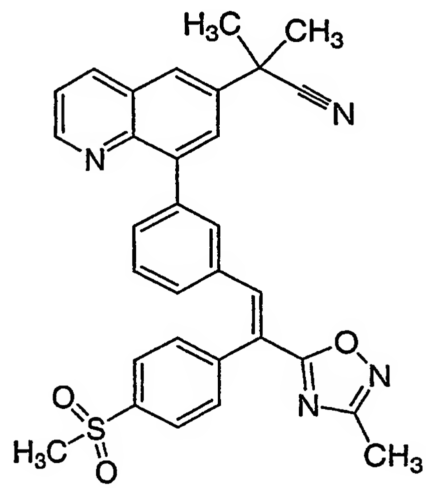
Example 21 was prepared by following the procedure described above for Examples 14 and 15 but substituting the aryl bromide **AB1** for **AB5** and the bromoquinoline **Q5** for **Q3** as the starting materials.

NMR ^{1}H (500MHz, Methanol) ∂ 8.8 (dd, 1H), 8.38 (dd, 1H), 8.04 (d, 2H), 7.88 (d, 2H), 7.66 (d, 1H), 7.55 (m, 4H), 7.36 (t, 1H), 7.29 (s, 1H), 7.18 (d, 1H), 2.93 (s, 3H), 1.88 (s, 6H).

MS (M-CO_2): 451.4 (negative ion).

EXAMPLE 22

2-methyl-2-[8-(3-{(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]propanenitrile



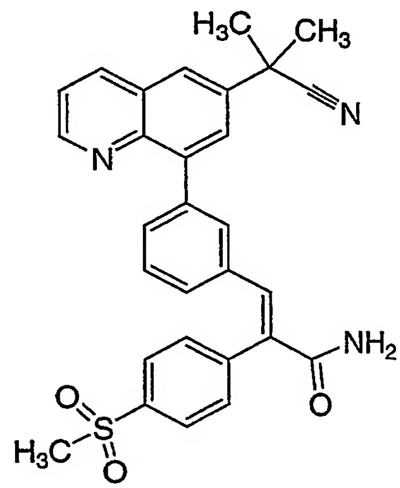
Example 22 was prepared by following the procedure described for Examples 14 and 15 using the aryl bromide **AB5** and substituting the bromoquinoline **Q5** for **Q3** as the starting materials.

NMR ^{1}H (500 MHz, Acetone-d_6) ∂ 8.90 (dd, 1H), 8.43 (dd, 1H), 8.1 (d, 2H), 8.01 (d, 2H), 7.83 (d, 1H), 7.71 (t, 3H), 7.66 (s, 1H), 7.56 (q, 1H), 7.55 (dd, 1H), 7.38 (t, 1H), 7.22 (d, 1H), 3.03 (s, 3H), 2.33 (s, 3H), 1.87 (s, 6H)

MS (M+1): 535.2

EXAMPLE 23

(E)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenamide

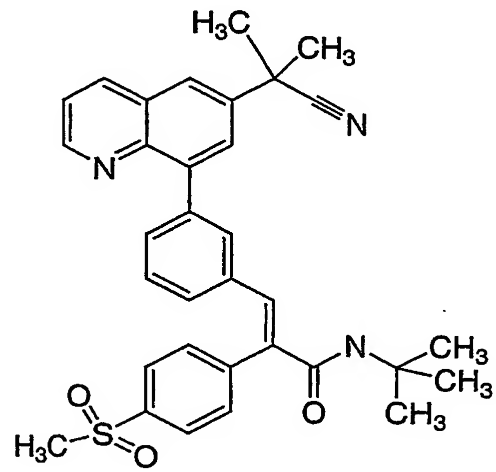


Example 23 was prepared by following the procedure described above for Examples 14 and 15 but substituting the aryl bromide **AB3** for **AB5** and the bromoquinoline **Q5** for **Q3** as the starting materials, the title compound was obtained.

NMR ^{1}H (500MHz, Acetone-d_6) ∂ 8.89 (dd, 1H), 8.43 (dd, 1H), 8.08 (d, 1H), 7.93 (d, 2H), 7.8 (d, 2H), 7.6 (m, 4H), 7.48 (s, 1H), 7.31 (t, 1H), 7.08 (d, 1H), 6.6 (bs, 1H), 6.7 (bs, 1H), 2.93 (s, 3H), 1.87 (s, 6H)

EXAMPLE 24

(E)-N-(tert-butyl)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenamide



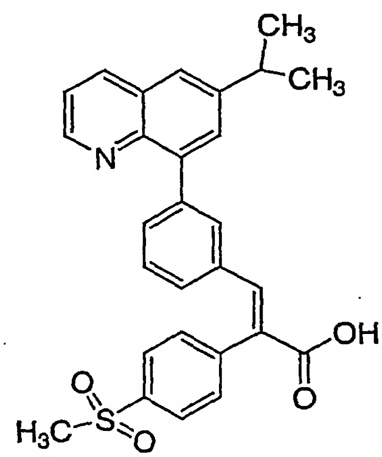
Example 24 was prepared by following the procedure described for Examples 14 and 15 but substituting the aryl bromide **AB4** for **AB5** and the bromoquinoline **Q5** for **Q3** as the starting materials.

NMR ^{1}H (500MHz, Acetone-d_6) ∂ 8.89 (dd, 1H), 8.43 (dd, 1H), 8.08 (d, 1H), 7.92 (d, 2H), 7.79 (d, 1H), 7.58 (m, 5H), 7.45 (s, 1H), 7.29 (t, 1H), 7.04 (d, 1H), 6.4 (bs, 1H), 2.93 (s, 3H), 1.87 (s, 6H), 1.36 (s, 9H).

MS (M + 1) 553.

EXAMPLE 25

(E)-3-[3-(6-isopropyl-8-quinolinyl)phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid



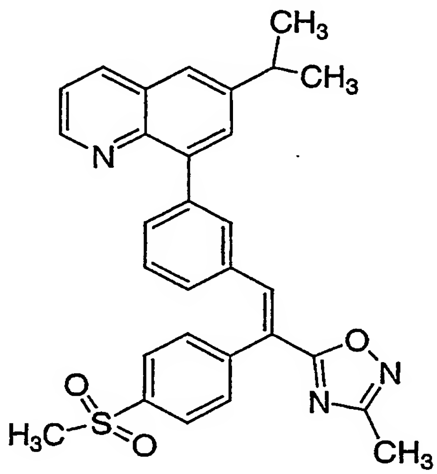
Example 25 was prepared by following the procedure described for Examples 14 and 15 but substituting the aryl bromide **AB1** for **AB5**, and 5-isopropyl-8-bromoquinoline (described in International Patent Publication WO9422852) for **Q3**, as the starting materials.

NMR ^{1}H (500MHz, Acetone-d_6) ∂ 8.69 (dd, 1H), 8.26 (dd, 1H), 7.85 (s, 1H), 7.83 (d, 2H), 7.68 (s, 1H), 7.51 (d, 2H), 7.49 (m, 2H), 7.36 (dd, 1H), 7.31 (t, 1H), 7.20 (s, 1H), 7.13 (d, 1H), 3.1 (m, 1H), 2.93 (s, 3H), 1.36 (d, 6H).

MS (M + 1) 472.

EXAMPLE 26

6-isopropyl-8-(3-{(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline



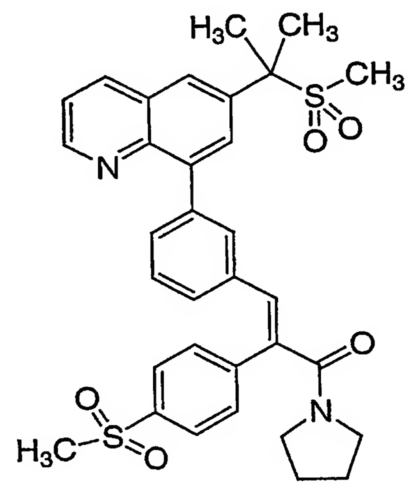
Example 26 was prepared by following the procedure described for Examples 14 and 15 using the aryl bromide **AB5**, and substituting 5-isopropyl-8-bromoquinoline (described in International Patent Publication WO9422852) for **Q3** as the starting materials.

NMR ^{1}H (500MHz, Acetone-d_6) ∂ 8.80 (dd, 1H), 8.29 (dd, 1H), 8.12 (s, 1H), 8.03 (d, 2H), 7.76 (s, 1H), 7.73 (m, 3H), 7.59 (s, 1H), 7.53 (d, 1H), 7.47 (q, 1H), 7.36 (t, 1H), 7.22 (d, 1H), 3.1 (m, 1H), 2.93 (s, 3H), 2.33 (s, 3H) 1.36 (d, 6H).

MS (M+1) 510.

EXAMPLE 27

(E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-2-propen-1-one



Example 27 was prepared by the following procedure.

Step 1: (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid

A mixture of 3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}benzaldehyde from step 4 of Example 18 (2.33g, 6.60mmol), 4-(methylsulfonyl)phenyl acetic acid (1.71g, 7.98mmol) and piperidine (0.20ml, 1.98mmol) in 10mL of toluene was refluxed for 2 days. The mixture was cooled to r.t., diluted with CH_2Cl_2, subjected to flash chromatography (CH_2Cl_2/EtOAc/AcOH, 50/50/1) and finally stirred with (Et_2O/CH_2Cl_2) and isolated to give (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid (single isomer) as a white solid.

NMR ^1H (400MHz, Acetone-d_6): ∂ 8.89 (dd, 1H), 8.39 (dd, 1H), 8.07 (d, 1H), 8.03 (d, 2H), 7.94 (s, 1H), 7.86 (d, 1H), 7.71-7.68 (m, 3H) 7.62-7.60 (m, 2H), 7.55 (dd, 1H), 7.45 (s, 1H) 7.34 (t, 1H), 7.18 (d, 1H), 4.67 (q, 1H), 3.04 (s, 3H), 2.86 (s, 3H) 1.88 (s,3H).

MS (M + 1) 576.

Step 2: (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-2-propen-1-one

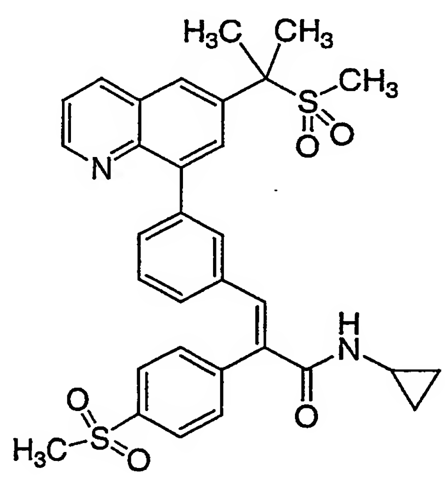
A mixture of (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid (104mg, 0.19mmol) from the present step 1 above, pyrrolidine (24µL, 0.29mmol), EDCI (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (55mg, 0.29mmol) and HOBt (1-Hydroxybenzotriazole hydrate) (34mg, 0.25mmol) in 1ml of DMF was stirred at r.t. for 12h. The mixture was diluted with EtOAc, washed with NH_4Cl (sat), H_2O (3x), brine, dried over Na_2SO_4, filtered and concentrated. Stirring in EtOAc/Hex yielded Example 27 as a white solid.

NMR ^1H (400MHz, Acetone-d_6): ∂ 8.88 (dd, 1H), 8.40 (dd, 1H), 8.22 (d, 1H), 8.98 (d, 1H), 7.88 (d, 2H), 7.67 (d, 2H), 7.60 (d, 1H) 7.55-7.52 (m, 2H) 7.34 (t, 1H), 7.18 (d, 1H), 7.03 (bs, NH) 3.58 (bs, 2H), 3.44 (bs, 2H), 3.02 (s, 3H), 2.69 (s, 3H) 1.95 (s, 6H), 1.88 (bs, 4H).

MS (M + 1) 603.

EXAMPLE 28

(E)-N-cyclopropyl-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide



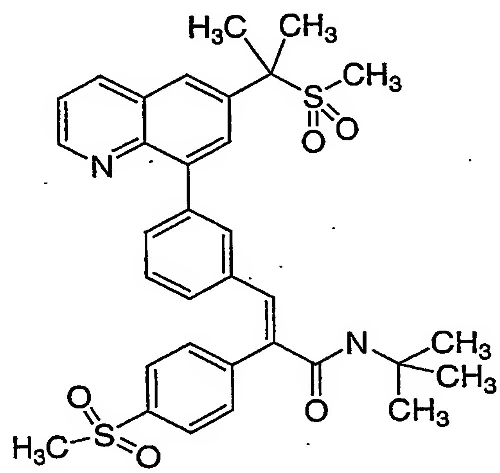
Example 28 was prepared by following the procedure for step 2 of Example 27 but substituting cyclopropyl amine for pyrrolidine, thus yielding a white solid.

NMR ^{1}H (400 MHz, acetone-d_6): ∂ 8.89 (dd, 1H), 8.41 (dd, 1H), 8.23 (d, 1H), 7.98 (d, 1H), 7.87 (d, 2H), 7.68 (s, 1H), 7.59-7.53 (m, 4H), 7.43 (s, 1H), 7.29 (t, 1H), 7.04 (d, 1H), 6.94 (bs, 1H), 2.89 (s, 3H), 2.84-2.80 (m, 1H), 2.69 (s, 3H), 1.96 (s, 6H), 0.67-0.63 (m, 2H), 0.49-0.45 (m, 2H).

MS (M + 1) 589.

EXAMPLE 29

(E)-N-(tert-butyl)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide



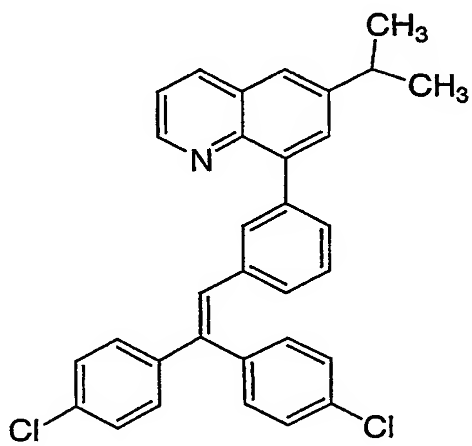
Example 29 was prepared as a white solid by following the procedure for step 2 of Example 27 but substituting *t*-butyl amine amine for pyrrolidine.

NMR ^{1}H (400MHz, acetone-d_6): ∂ 8.89 (dd, 1H), 8.41 (dd, 1H), 8.23 (d, 1H), 7.98 (d, 1H), 7.90 (d, 2H), 7.59-7.53 (m, 5H), 7.43 (s, 1H), 7.30 (t, 1H), 7.05 (d, 1H), 6.43 (bs, 1H), 2.94 (s, 3H), 2.69 (s, 3H), 1.96 (s, 6H) , 1.36 (s, 9H)

MS (M+1) 606.

EXAMPLE 30

8-{3-[2,2-bis(4-chlorophenyl)vinyl]phenyl}-6-isopropylquinoline

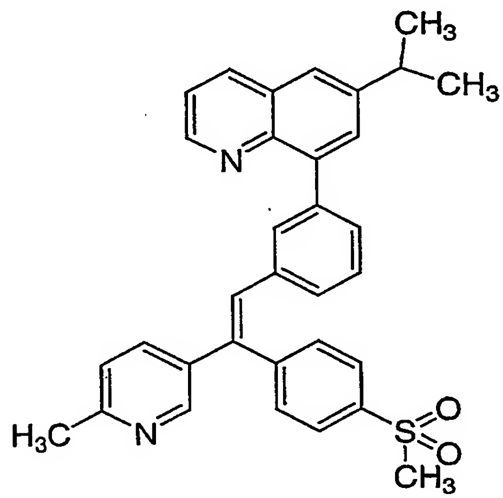


Example 30 was prepared by the following procedure. To a mixture of the benzylphosphonate **P2** (100mg, 0.25mmol), 4,4'-dichlorobenzophenone (63mg, 0.25mmol),) in THF (2mL) at r.t. was added potassium *t*-butoxide (1M, THF, 0.35mL, 0.35mmol). After 1h at r.t., the mixture was diluted with water/NH_4Cl and extracted with EtOAc. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 8:2) yielded Example 30 as a white foam.

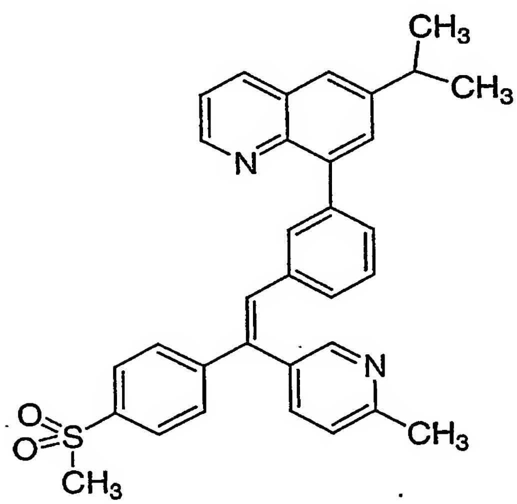
NMR ^1H (300MHz, acetone-d_6) ∂ 8.79 (dd, 1H), 8.28 (dd, 1H), 7.74 (d, 1H), 7.60 (d, 1H), 7.48-7.25 (m, 12H), 7.20-7.16 (m, 2H) 3.13 (hept, 1H), 1.36 (d, 6H).

EXAMPLES 31 AND 32

6-isopropyl-8-(3-{(E/Z)-2-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline



Example 31



Example 32

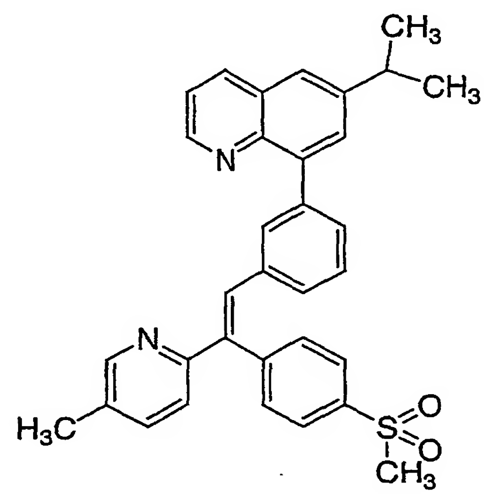
Examples 31 and 32 were prepared by following the procedure described for Example 30 but substituting the ketone **K7** for 4,4'-dichlorobenzophenone and using the benzylphosphonate **P2** as the starting materials.

NMR ^{1}H (300MHz, Acetone-d_6) (E) isomer (Example 31): ∂ 8.79 (dd, 1H), 8.43 (d, 1H), 8.27 (dd, 1H), 7.95 (d, 2H), 7.73 (d, 1H), 7.57-7.43 (m, 7H), 7.32-7.19 (m, 3H), 7.10 (d, 1H), 3.15 (hept, 1H), 2.98 (s, 3H), 1.34 (d, 6H).

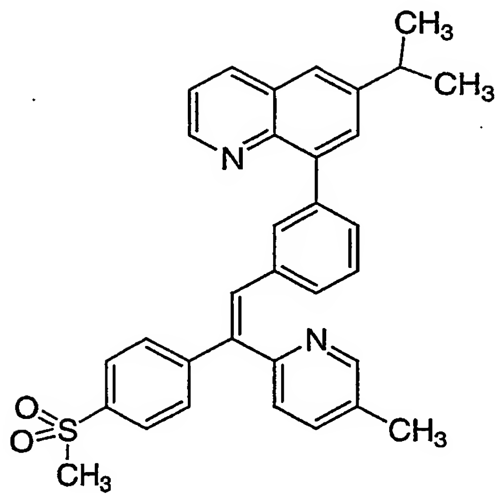
(Z) isomer (Example 32): ∂ 8.79 (dd, 1H), 8.35 (d, 1H), 8.28 (dd, 1H), 7.92 (d, 2H), 7.74 (d, 1H), 7.61-7.30 (m, 10H), 7.19 (d, 1H), 3.13 (s, 3H), 3.11 (hept, 1H), 1.35 (d, 6H).

EXAMPLES 33 AND 34

6-isopropyl-8-(3-{(E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline



Example 33



Example 34

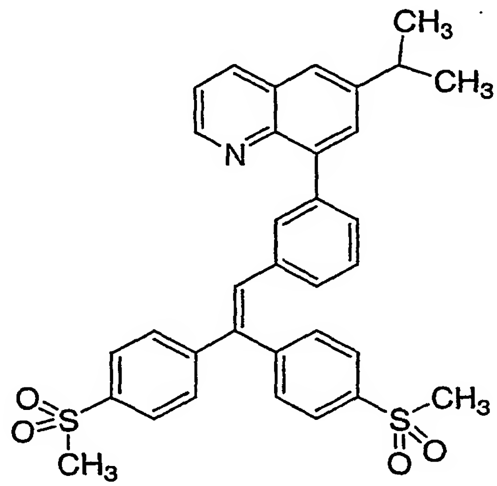
Examples 33 and 34 were prepared by following the procedure described for Example 30 but substituting the ketone **K8** for 4,4'-dichlorobenzophenone and using the benzylphosphonate **P2** as the starting materials.

NMR ^{1}H (300MHz, Acetone-d_6) (E) isomer (Example 33): ∂ 8.80 (dd, 1H), 8.48 (s, 1H), 8.28 (dd, 1H), 7.99-7.96 (m, 3H), 7.97 (m, 1H), 7.74 (d, 1H), 7.61-7.44 (m, 6H), 7.27 (t, 1H), 7.07 (d, 1H), 6.97 (d, 1H), 3.15 (hept, 1H), 2.96 (s, 3H), 1.36 (d, 6H).

NMR ^{1}H (300MHz, Acetone-d_6) (Z) isomer (Example 34): ∂ 8.79 (dd, 1H), 8.52 (s, 1H), 8.29 (dd, 1H), 7.89 (d, 2H), 7.75 (d, 1H), 7.65-7.54 (m, 4H), 7.47 (dd, 1H), 7.42-7.23, (m, 5H), 7.11 (d, 1H), 3.12 (s, 3H), 3.12 (hept, 1H), 1.36 (d, 6H).

EXAMPLE 35

8-(3-{2,2-bis[4-(methylsulfonyl)phenyl]vinyl}phenyl)-6-isopropylquinoline

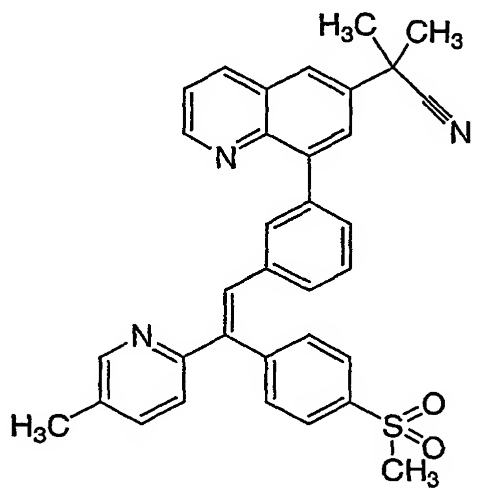


Example 35 was prepared by following the procedure described for Example 30 but substituting the ketone **K9** for 4,4'-dichlorobenzophenone and using the benzylphosphonate **P2** as the starting materials.

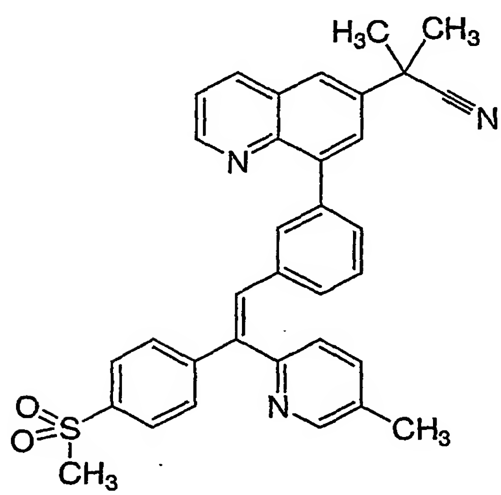
NMR ^{1}H (500MHz, Acetone-d_6): ∂ 8.80 (dd, 1H), 8.29 (dd, 1H), 7.98 (d, 2H), 7.93 (d, 2H), 7.75 (d, 1H), 7.61 (d, 2H), 7.59-7.56 (m, 3H), 7.50 (d, 1H), 7.48-7.44 (m, 3H) 7.30 (t, 1H), 7.12 (d, 1H), 3.14 (hept, 1H), 3.13 (s, 3H), 2.97(s, 3H), 1.35 (d, 6H).

EXAMPLES 36 AND 37

2-methyl-2-[8-(3-{(E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-quinolinyl]propanenitrile



Example 36



Example 37

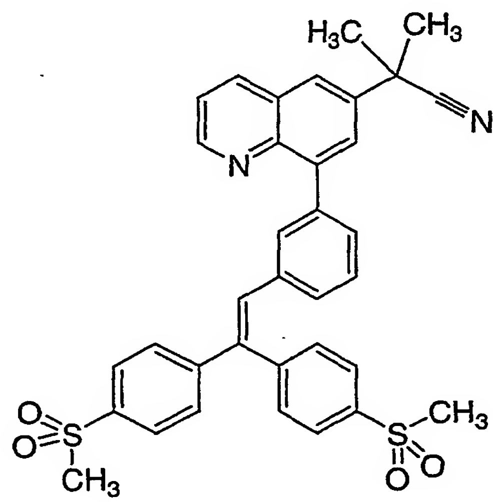
Examples 36 and 37 were prepared by following the procedure described for Example 30 but substituting the ketone **K8** for 4,4'-dichlorobenzophenone and substituting the benzylphosphonate **P3** for **P2** as the starting materials.

NMR ^{1}H (500MHz, Acetone-d_6) (E) isomer (Example 36): ∂ 8.90 (dd, 1H), 8.47 (s, 1H), 8.43 (dd, 1H), 8.08 (d, 1H), 8.00 (s, 1H), 7.97 (d, 2H), 7.83 (d, 1H) 7.57-7.53 (m, 5H), 7.50 (s, 1H), 7.28 (t, 1H), 7.06 (d, 1H), 6.96 (d, 1H), 2.96 (s, 3H), 2.33 (s, 3H), 1.88 (s, 6H).

NMR ^{1}H (300MHz, Acetone-d_6) (Z) isomer (Example 37): ∂ 8.89 (dd, 1H), 8.51 (s, 1H), 8.45 (dd, 1H), 8.09 (d, 1H), 7.89 (d, 2H), 7.72 (d, 1H), 7.62-7.56 (m, 5H), 7.43-7.42 (m, 2H) 7.30 (t, 1H), 7.25 (d, 1H), 7.10 (d, 1H), 3.11 (s, 3H), 2.34 (s, 3H), 1.87 (s, 6H).

EXAMPLE 38

2-[8-(3-{2,2-bis[4-(methylsulfonyl)phenyl]vinyl}phenyl)-6-quinolinyl]-2-methylpropanenitrile

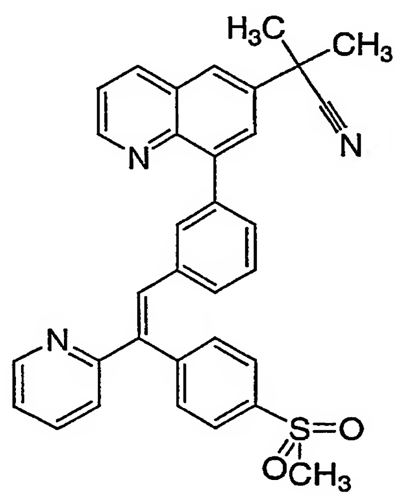


Example 38 was prepared by following the procedure described for Example 30 but substituting the ketone **K9** for 4,4'-dichlorobenzophenone and substituting the benzylphosphonate **P3** for **P2** as the starting materials.

NMR ^{1}H (500MHz, Acetone-d_6): ∂ 8.90 (dd, 1H), 8.44 (dd, 1H), 8.09 (d, 1H), 7.97 (d, 2H), 7.92 (d, 2H), 7.81 (d, 1H), 7.61 (d, 2H) 7.58-7.55 (m, 3H), 7.53 (s, 1H), 7.44 (s, 1H), 7.32 (t, 1H), 7.13 (d, 1H), 6.96 (d, 1H), 3.13 (s, 3H), 2.97 (s, 3H), 1.86 (s, 6H).

EXAMPLE 39

2-methyl-2-(8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(2-pyridinyl)ethenyl]phenyl}-6-quinolinyl)propanenitrile

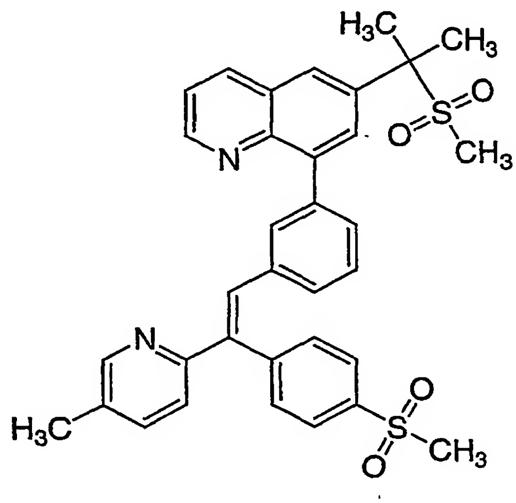


Example 39 was prepared by following the procedure described for Example 30 but substituting the ketone **K10** for 4,4'-dichlorobenzophenone and substituting the benzylphosphonate **P3** for **P2** as the starting materials.

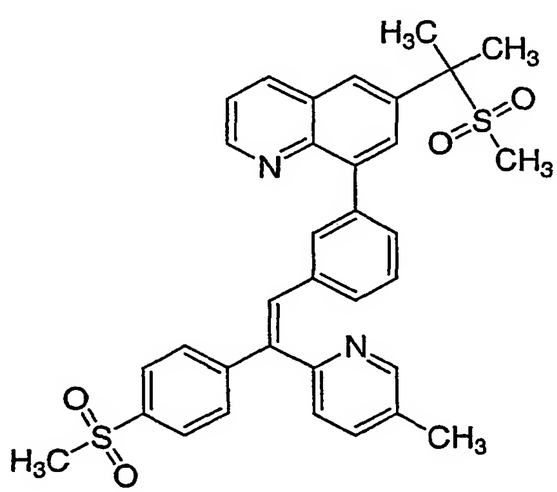
NMR ^{1}H (300MHz, Acetone-d_6): ∂ 8.90 (dd, 1H), 8.45 (dd, 1H), 8.11-8.09 (m, 2H), 7.84-7.80 (m, 3H), 7.72-7.69 (m, 1H), 7.63-7.52 (m, 5H), 7.43-7.38 (m, 2H), 7.33 (t, 1H) 7.28 (s, 1H), 7.14 (d, 1H), 2.97 (s, 3H), 1.86 (s, 6H)

EXAMPLES 40 AND 41

6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-{(E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)quinoline



Example 40



Example 41

Examples 41 and 42 were prepared by following the procedure described in Example 10 but substituting bromoquinoline **Q3** for **Q2** and substituting boronate **B3** for boronate **B2**.

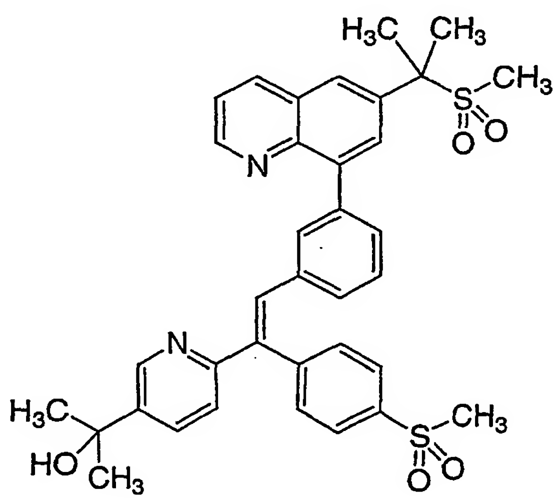
NMR ^{1}H (400MHz, Acetone-d_6) (E) isomer (Example 40): ∂ 8.91 (dd, 1H), 8.45 (s, 1H), 8.41 (dd, 1H), 8.23 (d, 1H), 8.01-8.00 (m, 2H), 7.95 (d, 2H), 7.57-7.54 (m, 4H), 7.51 (d, 1H) 7.49 (s, 1H), 7.28 (t, 1H), 7.07 (d, 1H), 6.96 (d, 1H), 2.94 (s, 3H), 2.69 (s, 3H), 2.33 (s, 3H), 1.97 (s, 6H).

NMR ^{1}H (400MHz, Acetone-d_6) (Z) isomer (Example 41): ∂ 8.88 (dd, 1H), 8.49 (s, 1H), 8.42 (dd, 1H), 8.24 (dd, 1H), 7.94 (d, 1H), 7.88 (d, 2H), 7.61-7.55 (m, 5H), 7.47 (s, 1H), 7.40 (s, 1H), 7.29 (t, 1H), 7.24 (d, 1H), 7.06 (d, 1H), 3.12 (s, 3H), 2.68 (s, 3H), 2.33 (s, 3H), 1.96 (s, 6H).

200
64

EXAMPLE 42

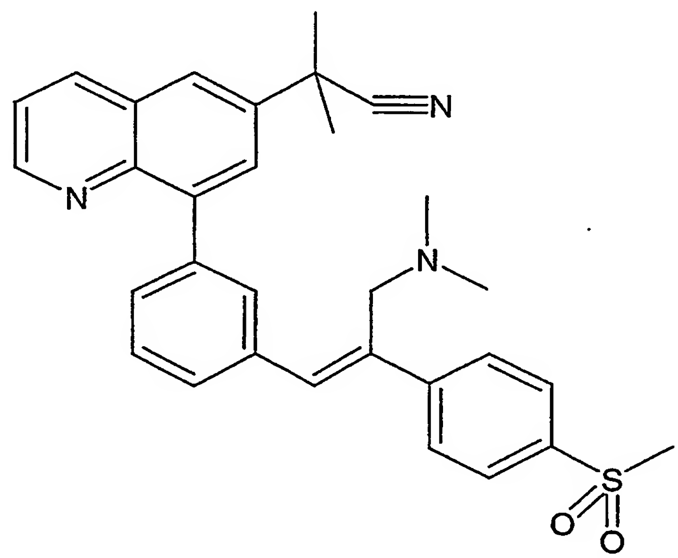
2-(6-{(E)-2-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl}-3-pyridinyl)-2-propanol



Example 42 was prepared by following the procedure described in Example 10 but substituting bromoquinoline **Q3** for **Q2** and substituting boronate **B4** for boronate **B2.**

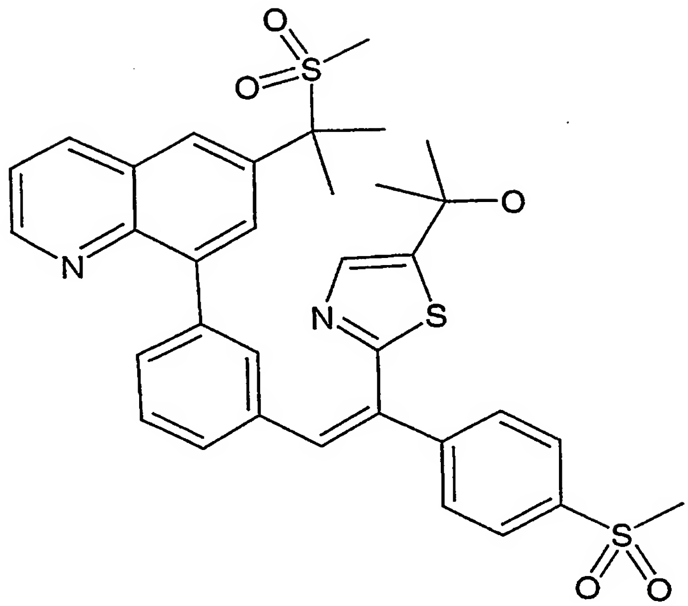
NMR ^{1}H (500 MHz, Acetone-d_6): ∂ 8.91 (dd, 1H), 8.80 (d, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.03-8.01 (m, 2H), 7.96 (d, 1H), 7.82 (dd, 1H), 7.58-7.54 (m, 4H), 7.51 (s, 1H), 7.29 (t, 1H), 7.08 (d, 1H), 7.01 (d, 1H), 4.31 (s, 1H), 2.96 (s, 3H), 2.70 (s, 3H), 1.96 (s, 6H), 1.56 (s, 6H).

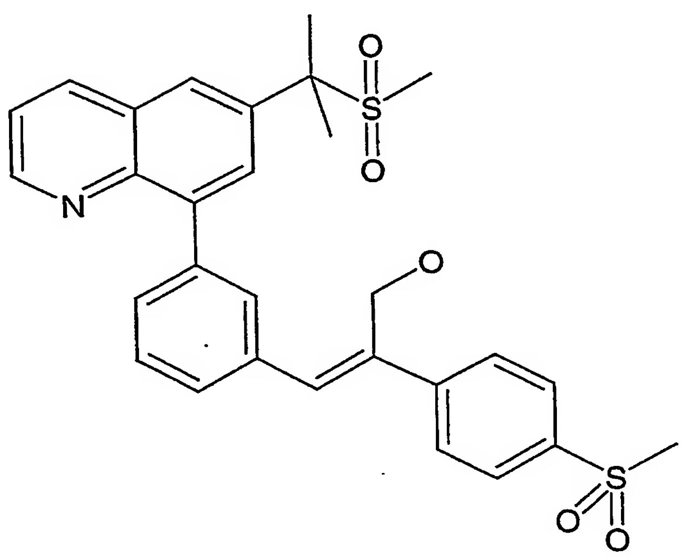
EXAMPLE 43

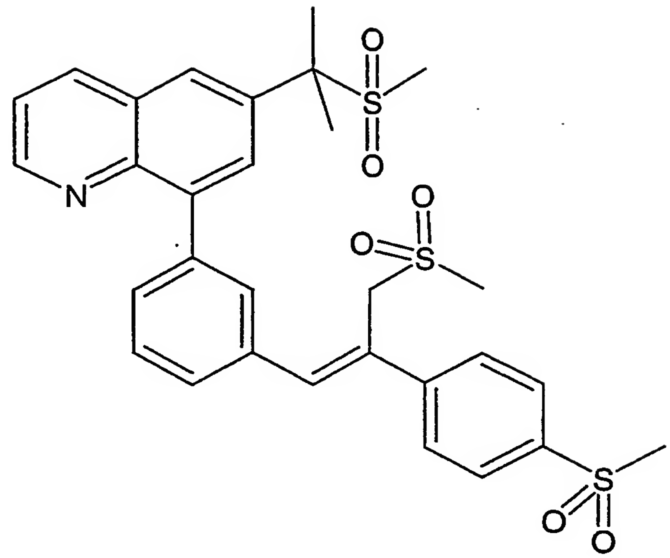


Example 43 was prepared following the procedure described previously for Examples 14 and 15 but substituting the aryl bromide **AB6** for **AB5** and the bromoquinoline **Q5** for **Q3** as the starting materials.

Additional Examples are the following:



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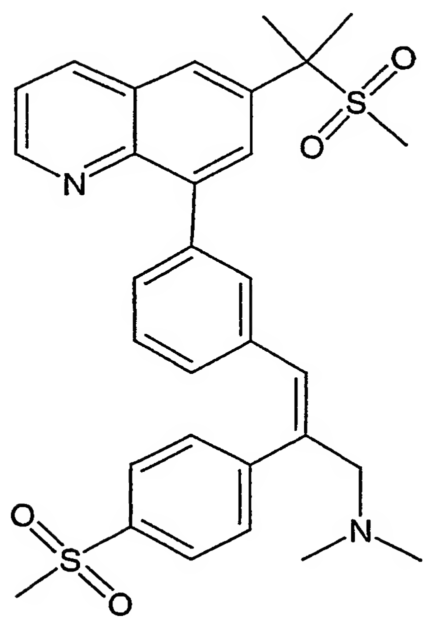
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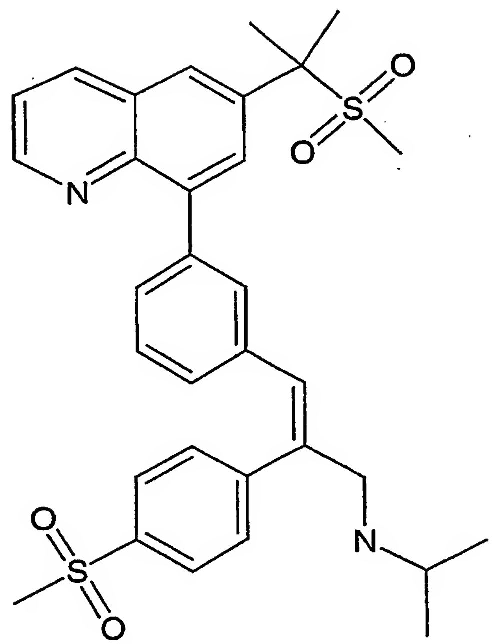

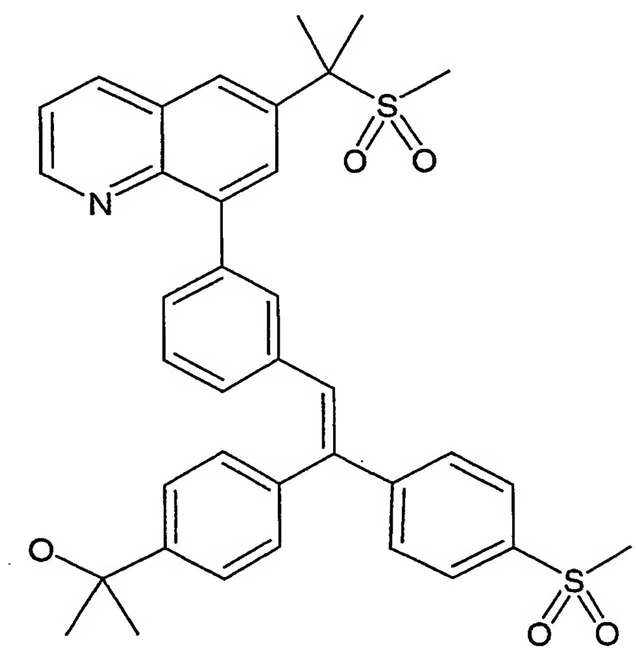

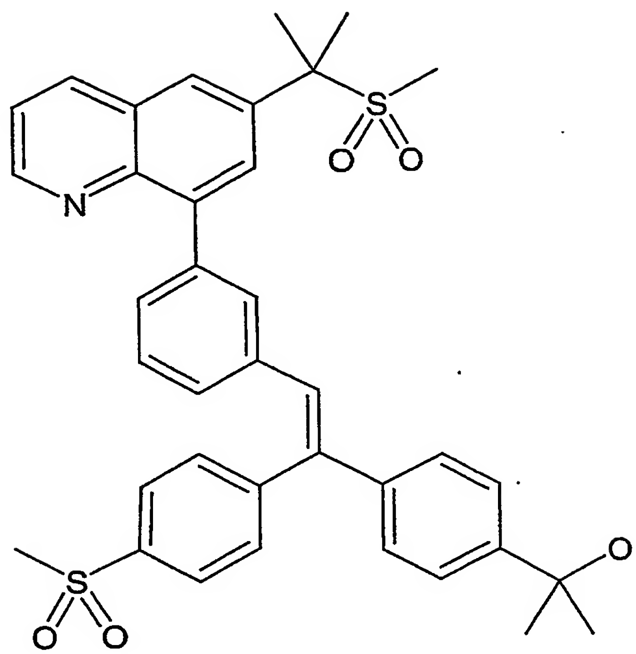

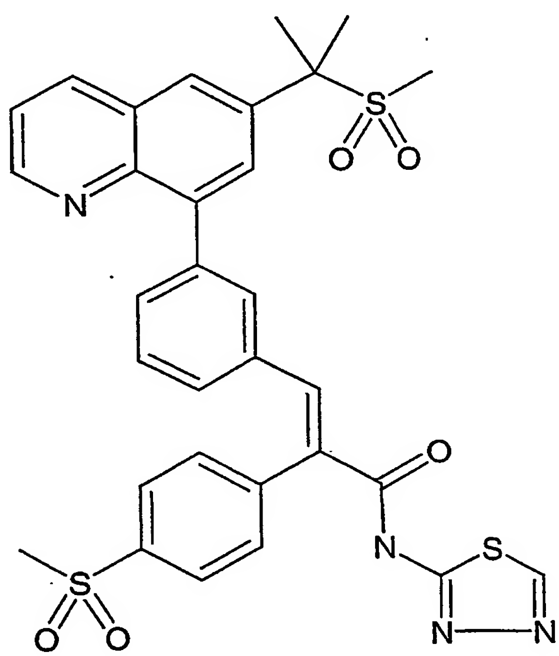

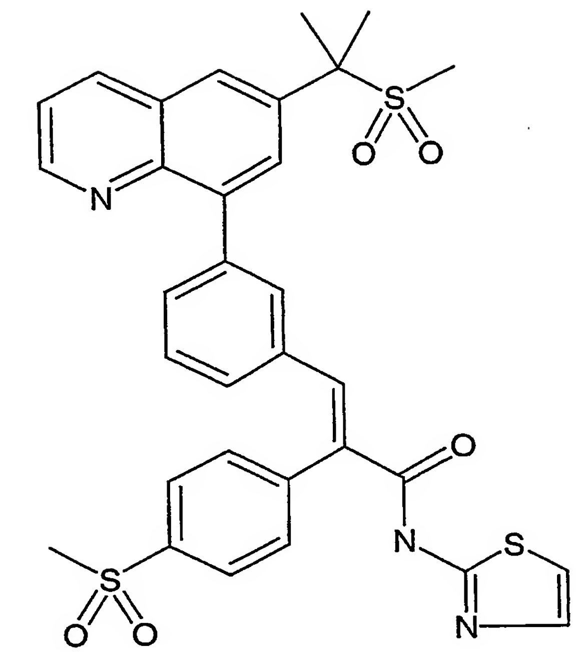

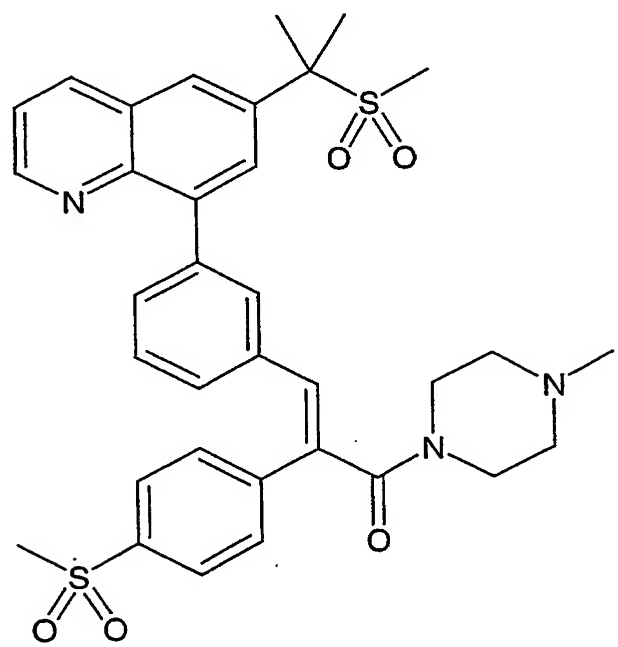

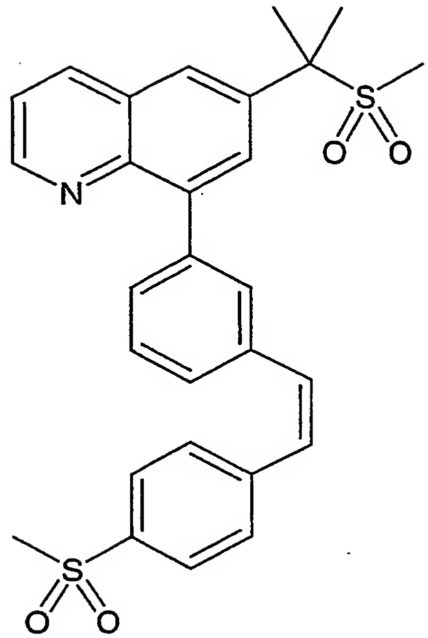

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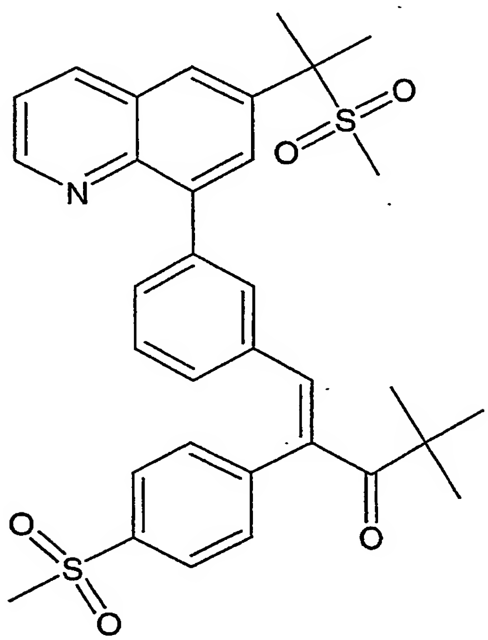

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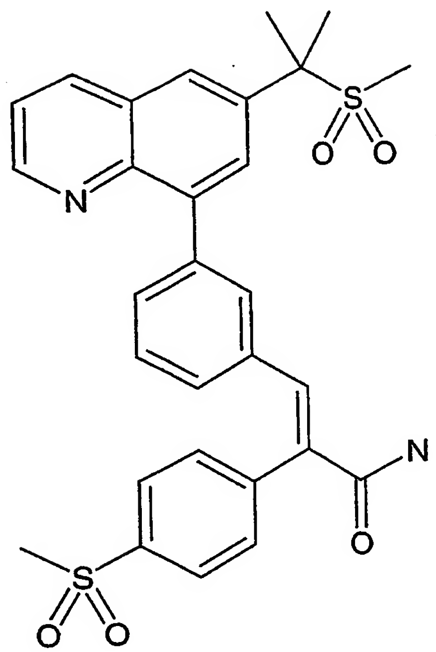

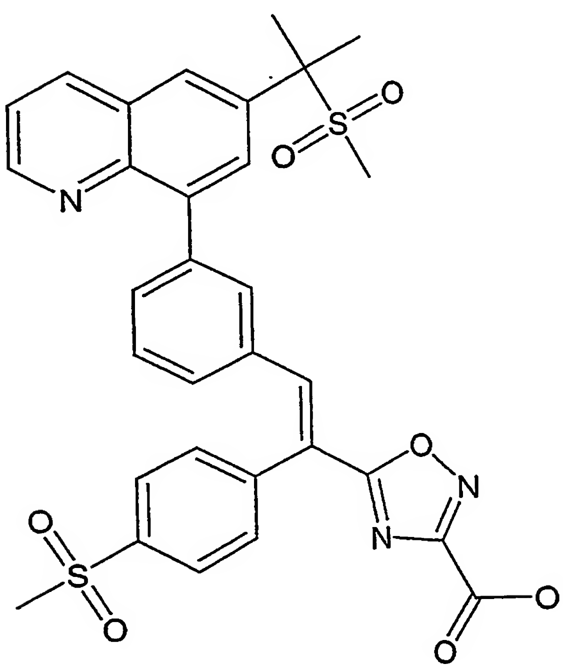

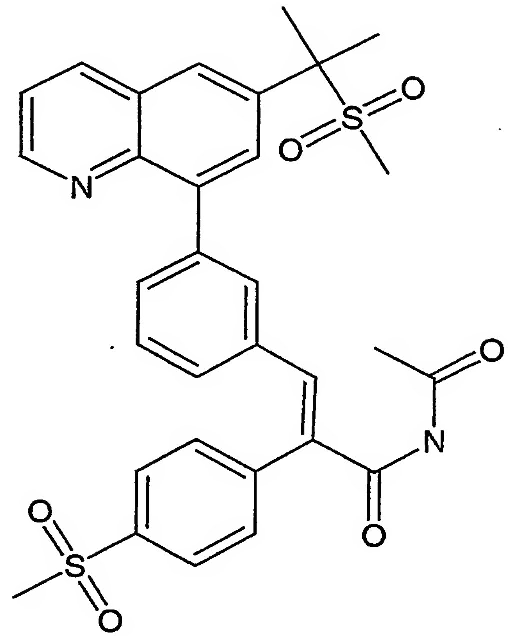
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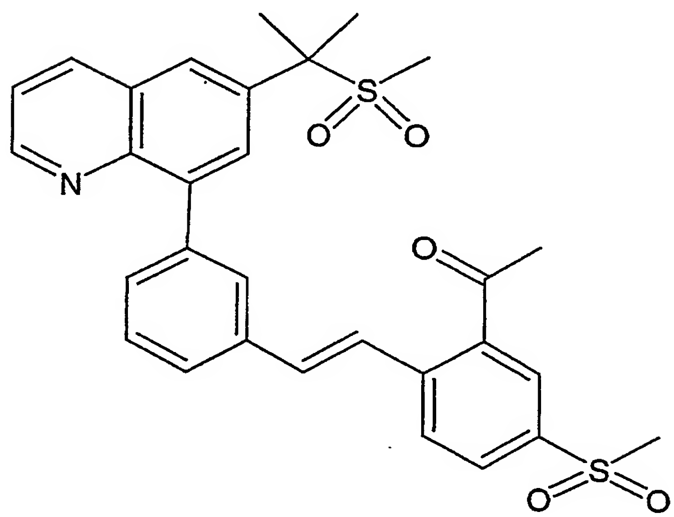
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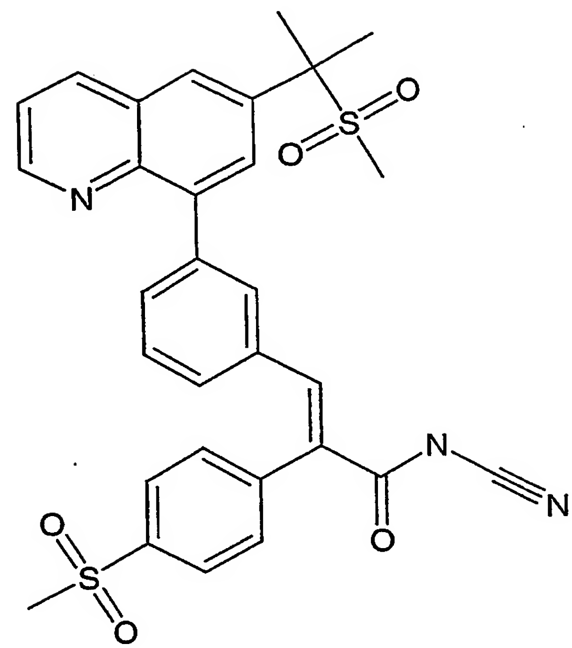
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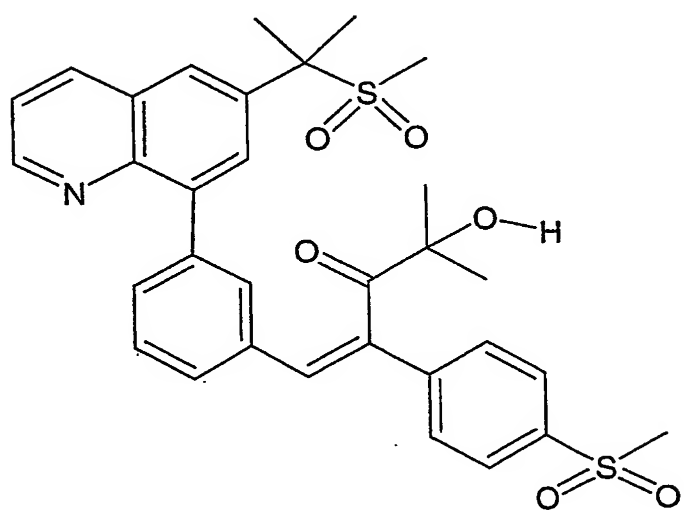
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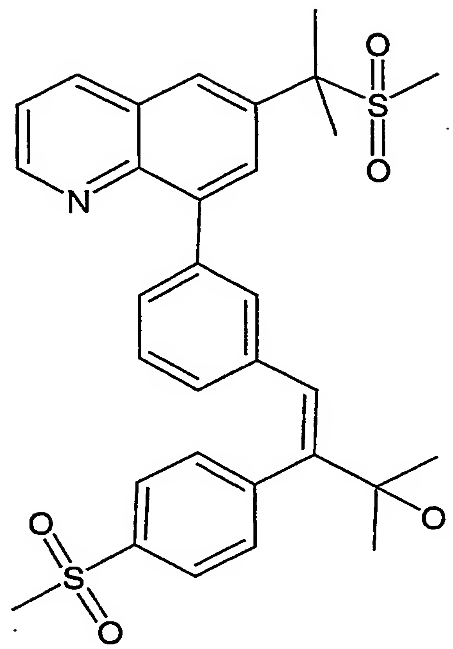

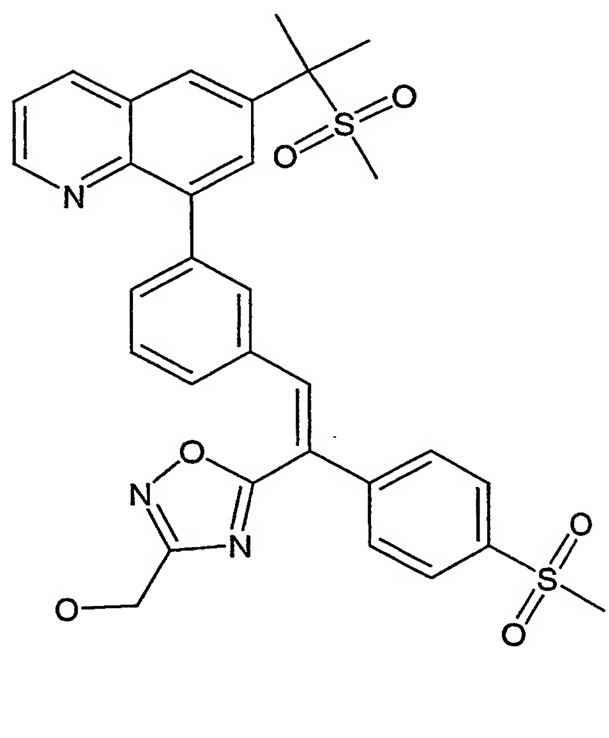

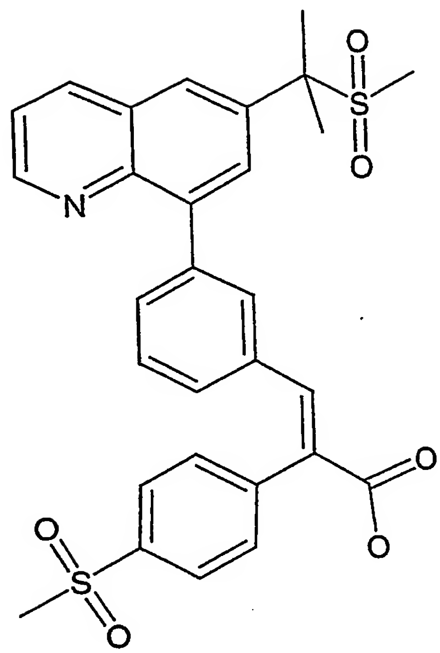
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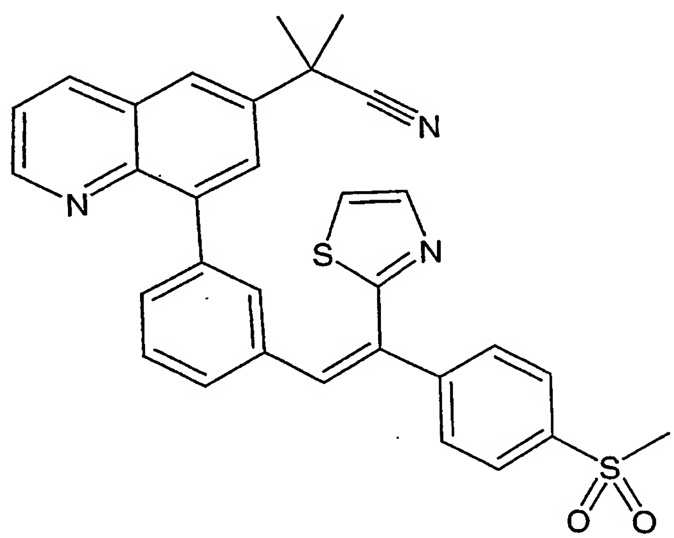
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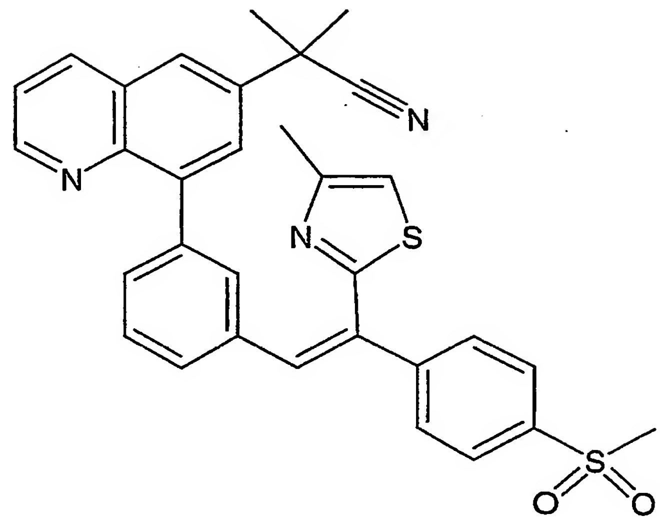
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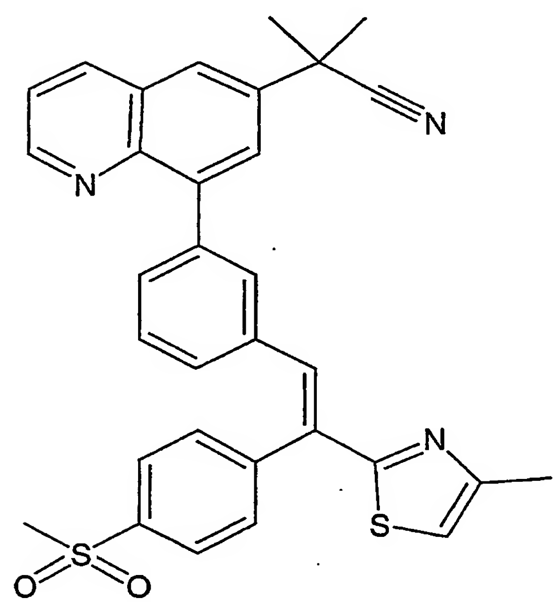
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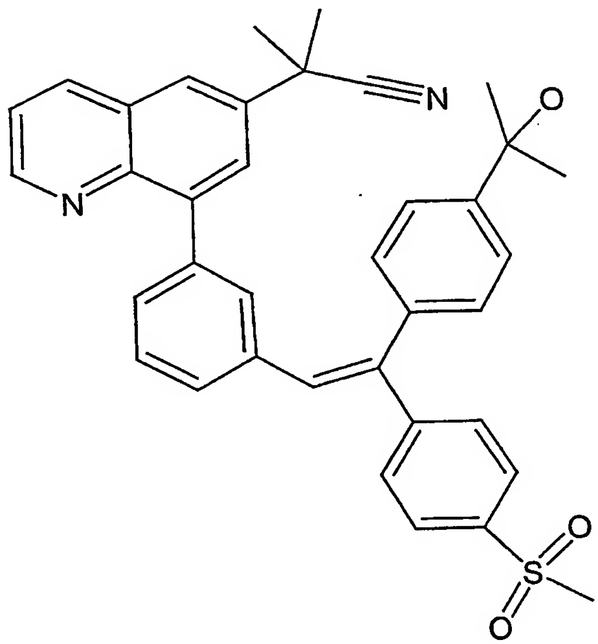

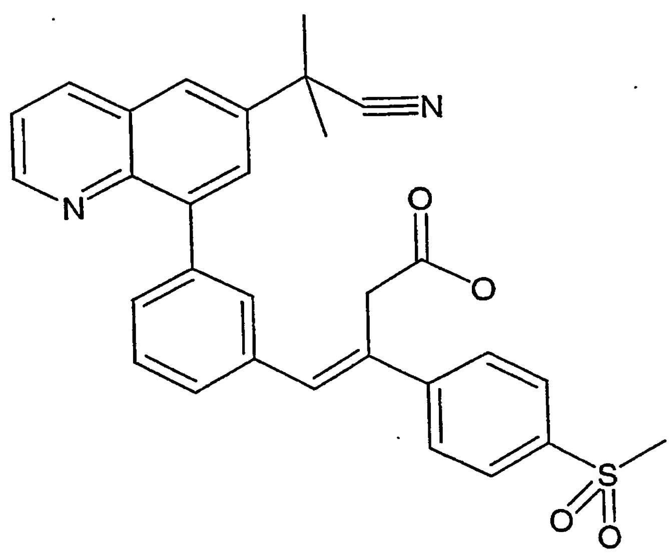

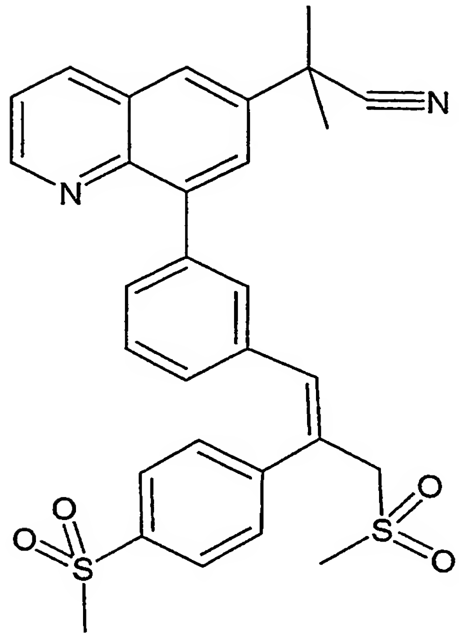

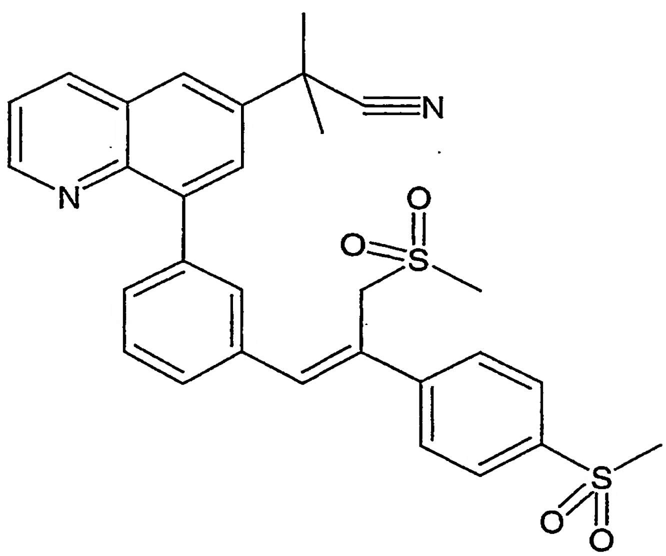

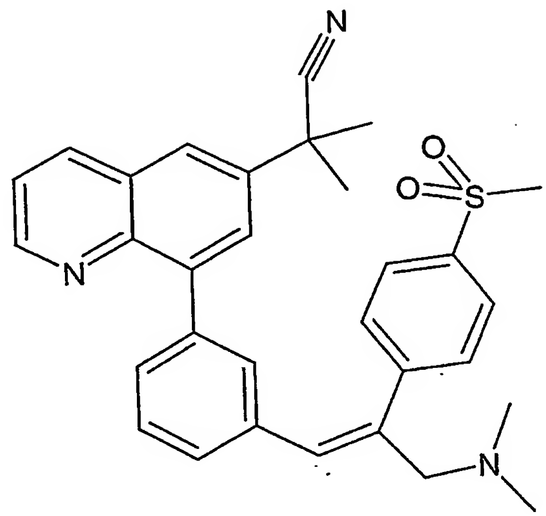
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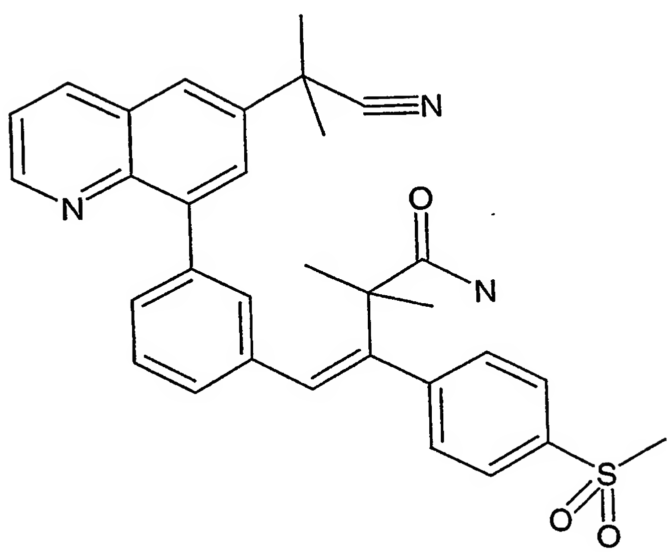
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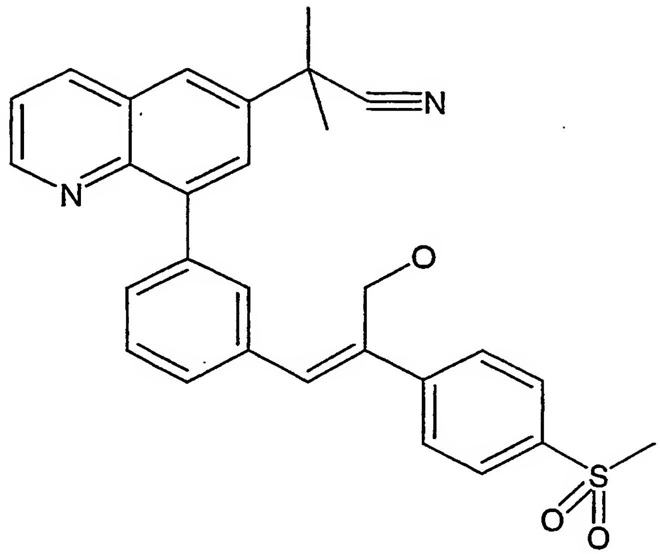
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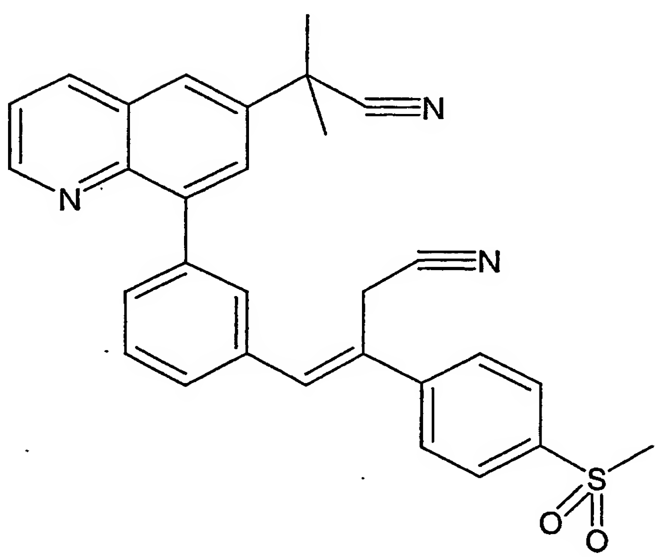
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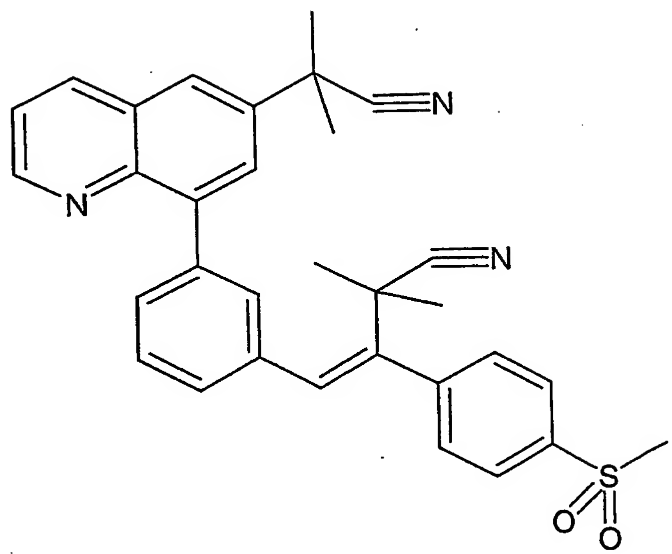
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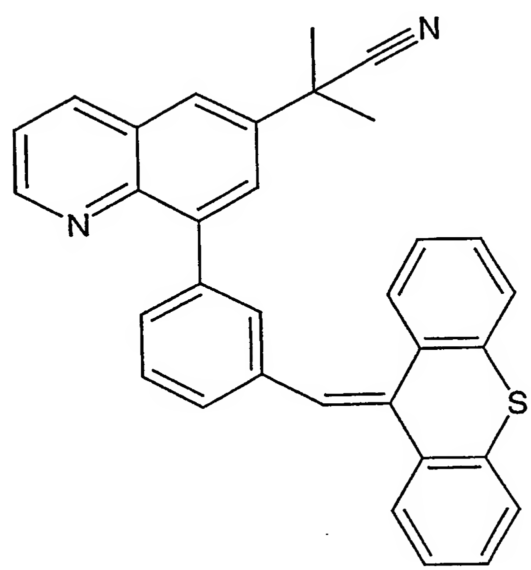
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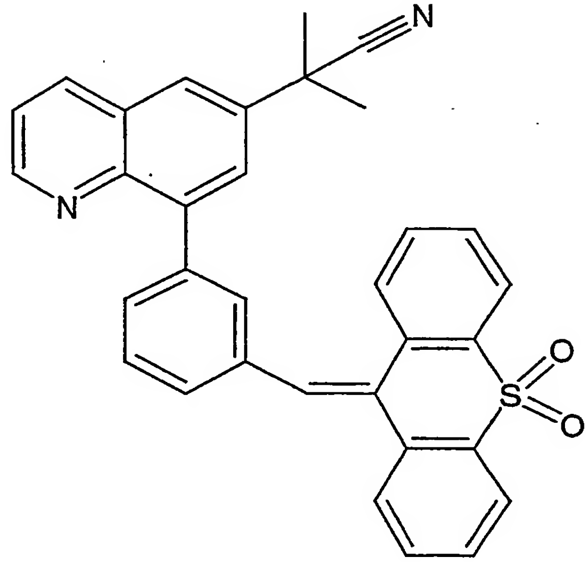
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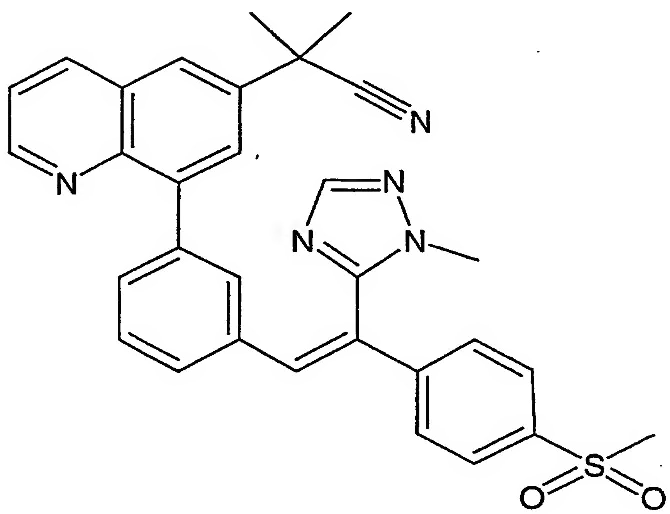
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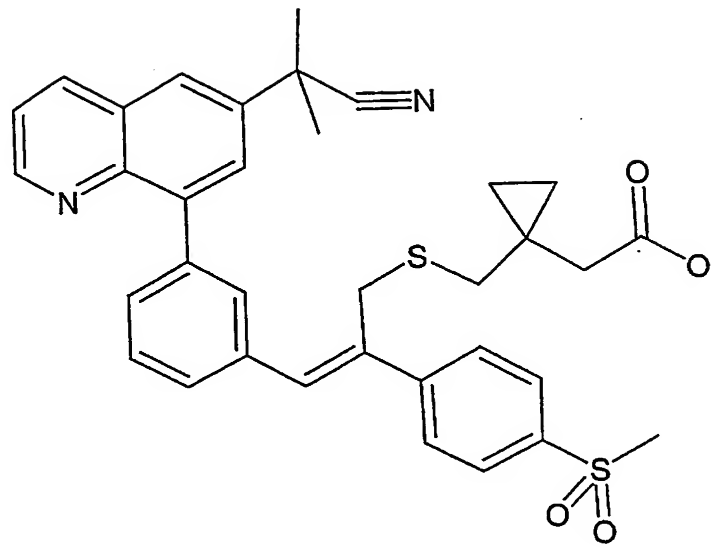
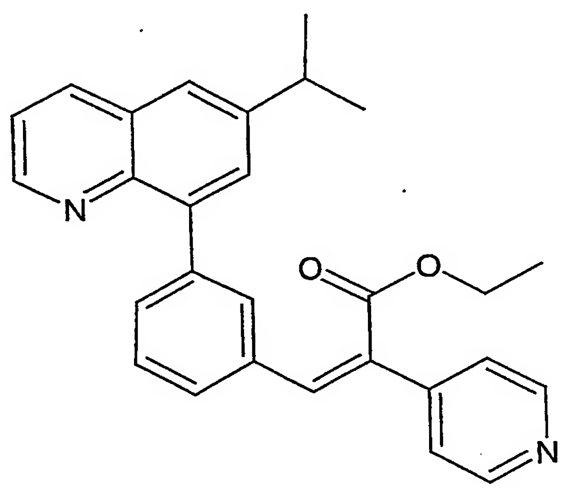
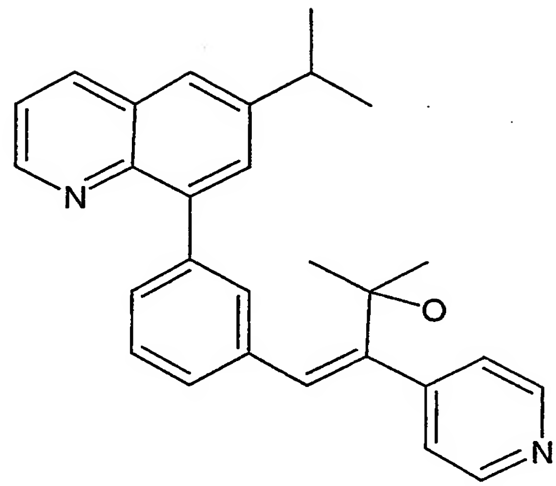
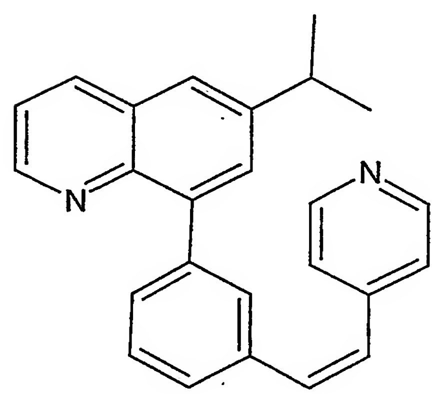
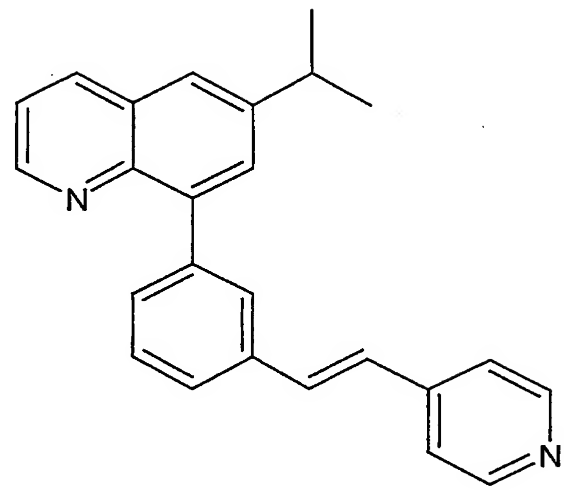


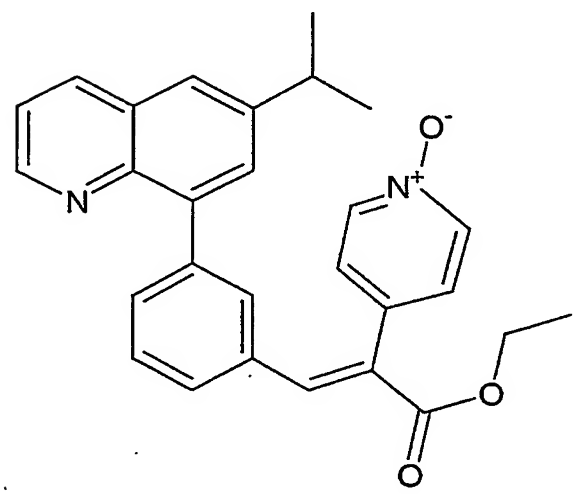


SUBSTITUTE SHEET (RULE 26)









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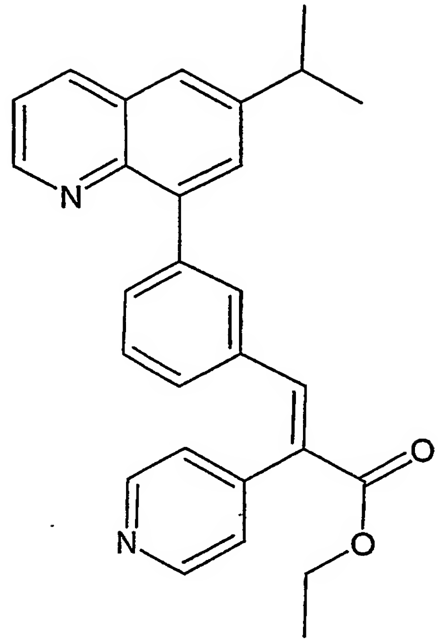
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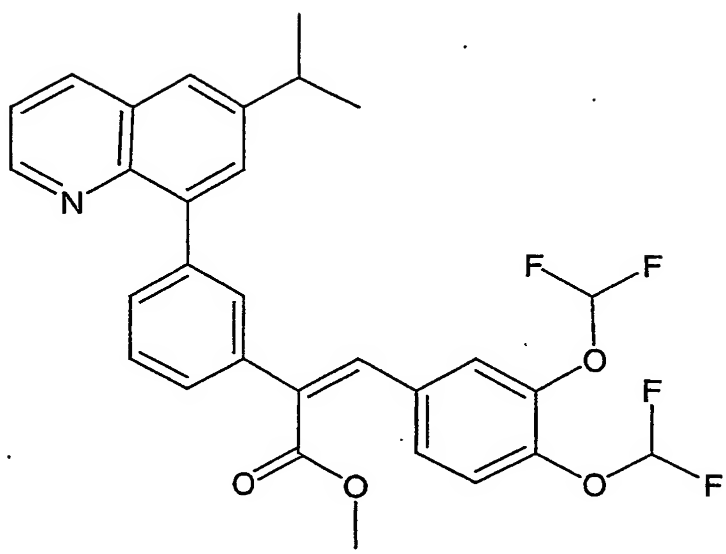
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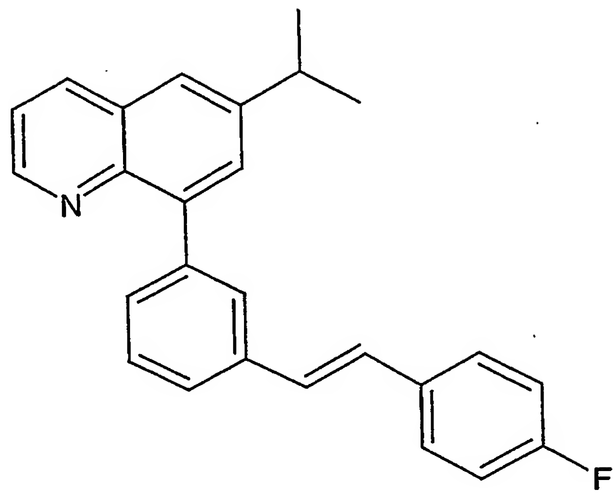
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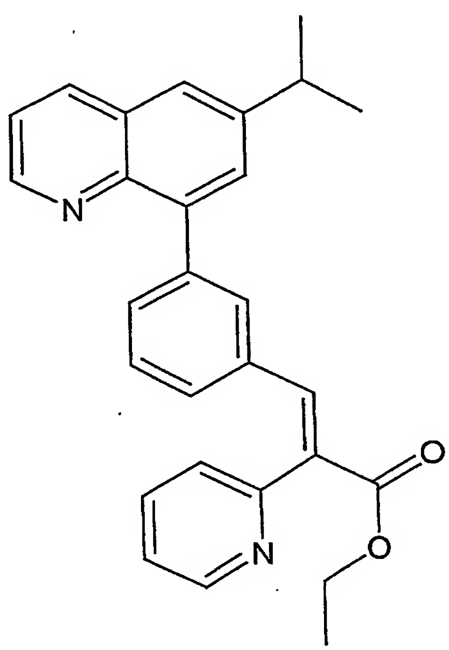
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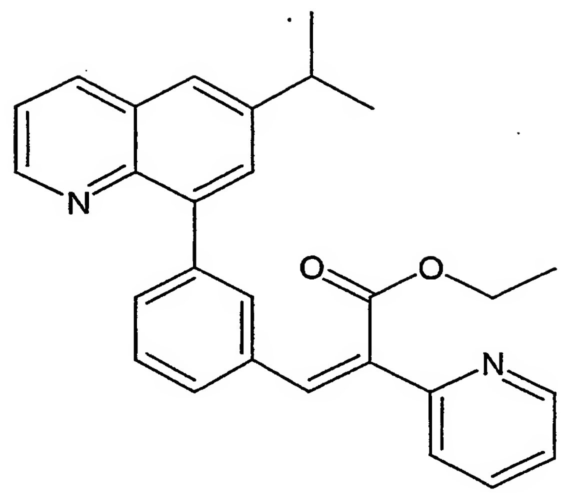

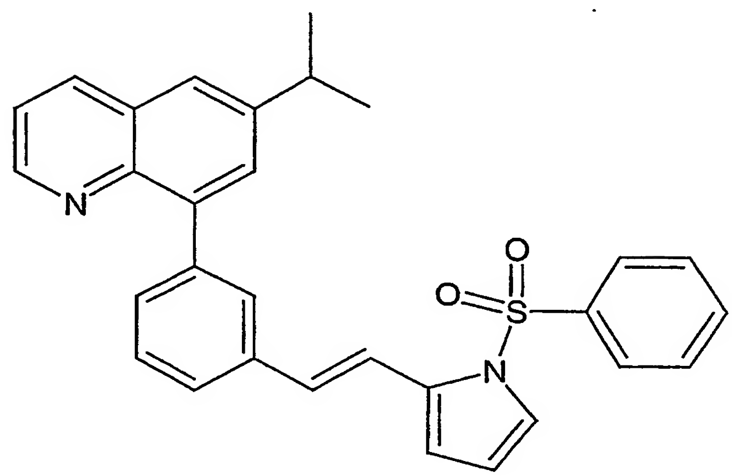

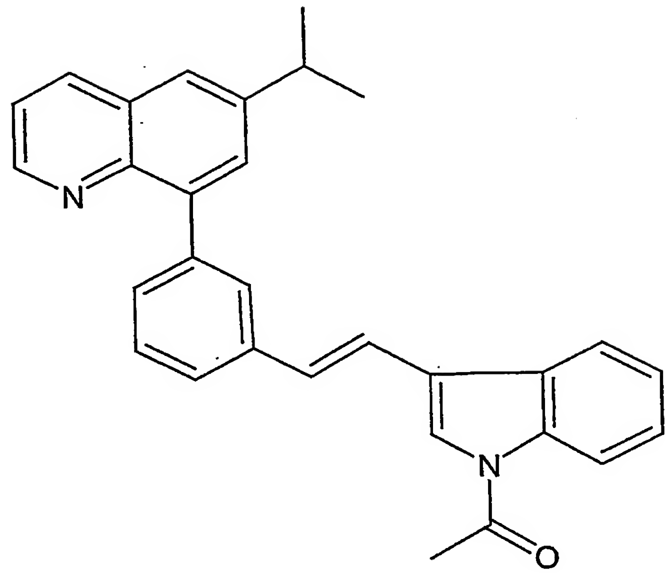

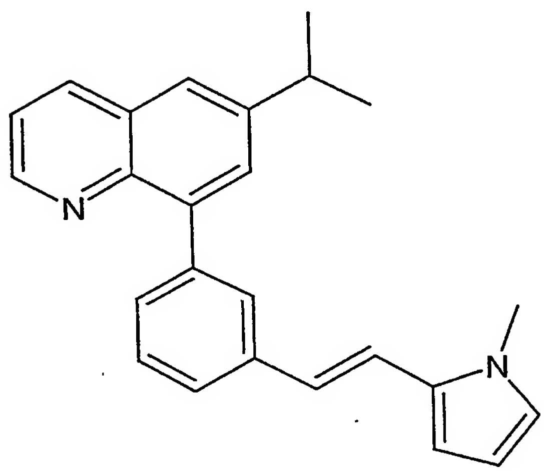

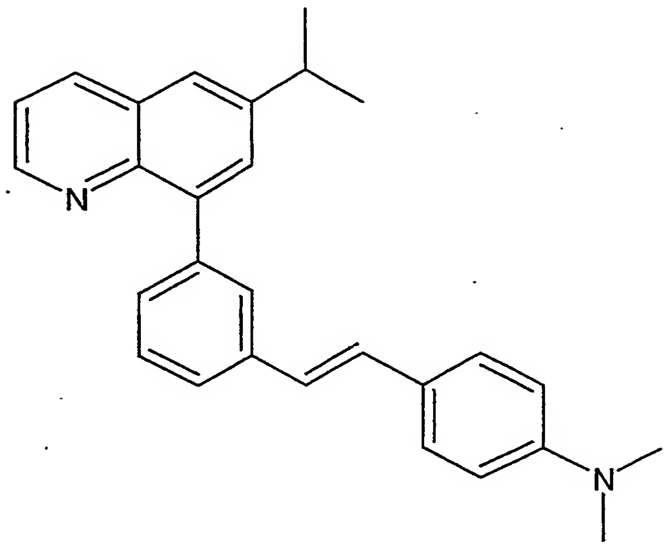
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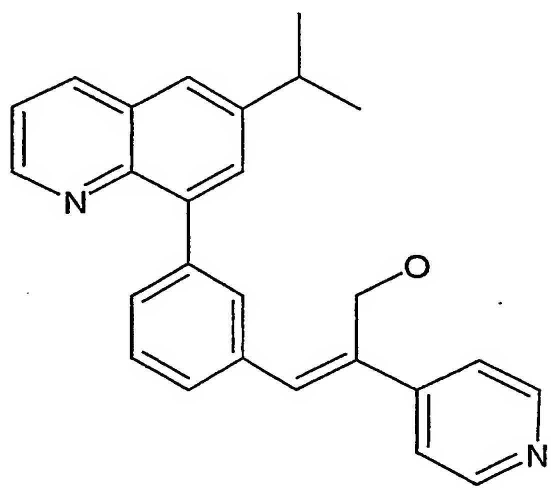
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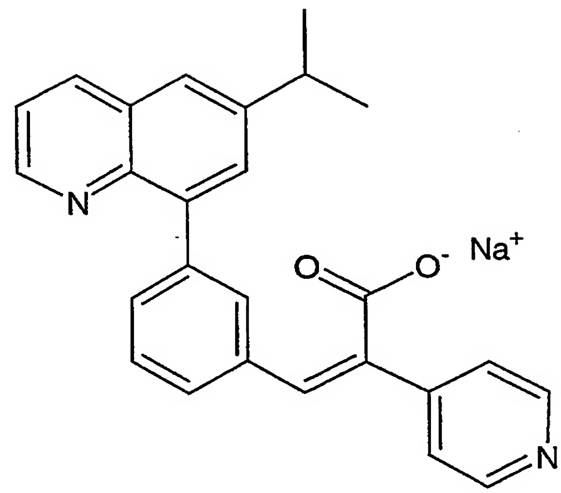

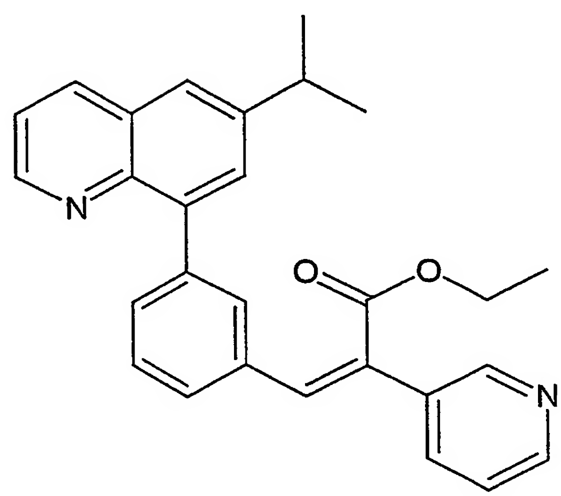

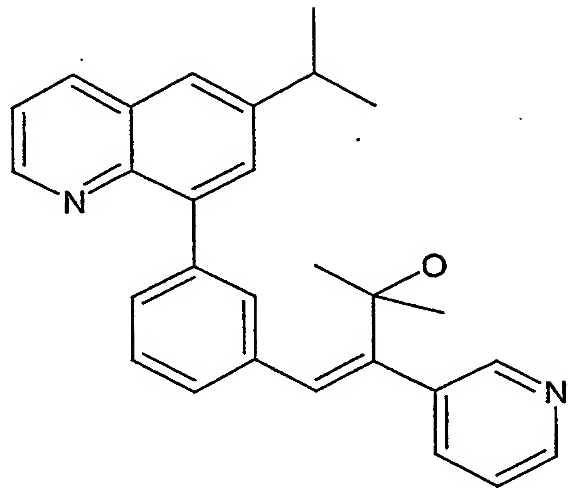

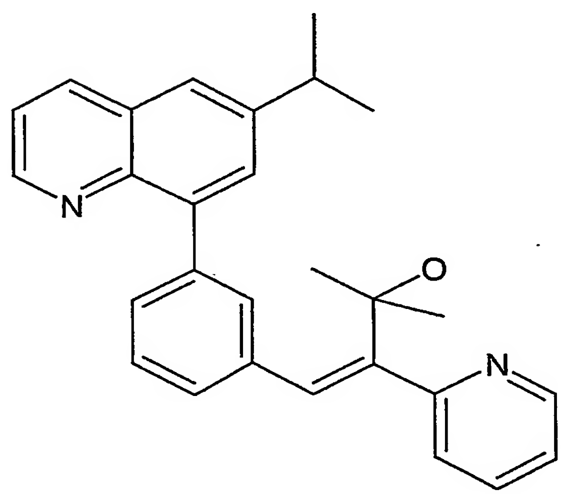

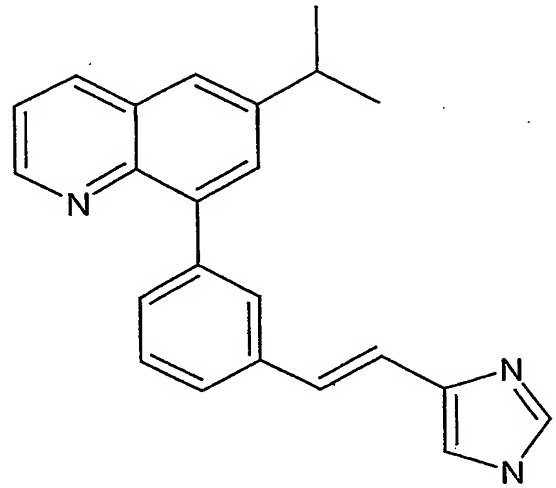
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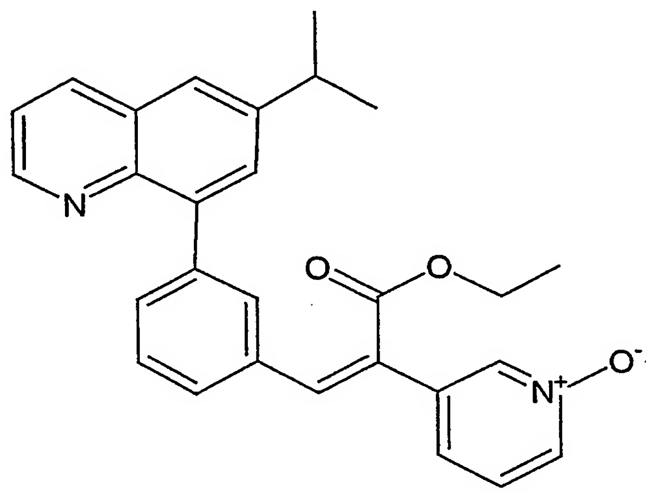
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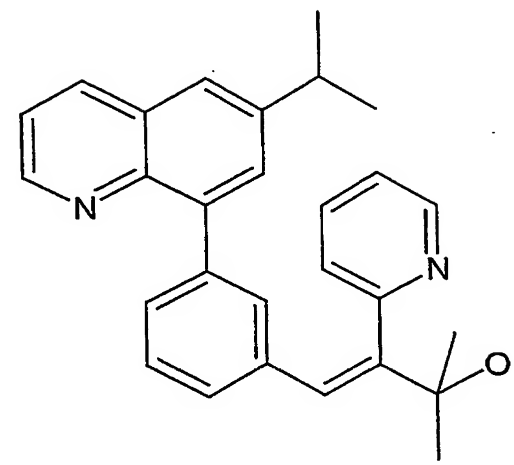
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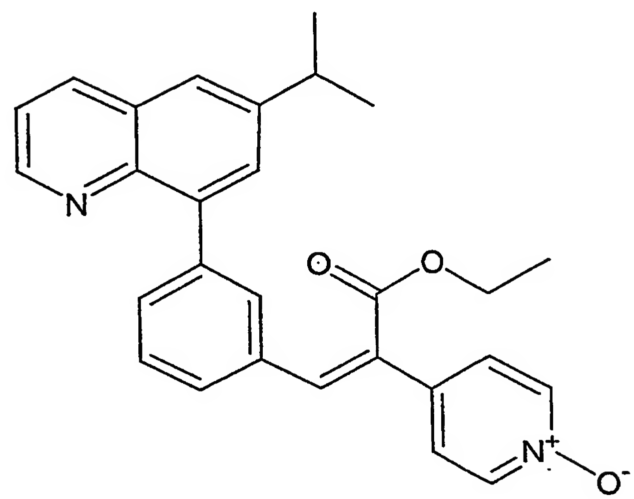
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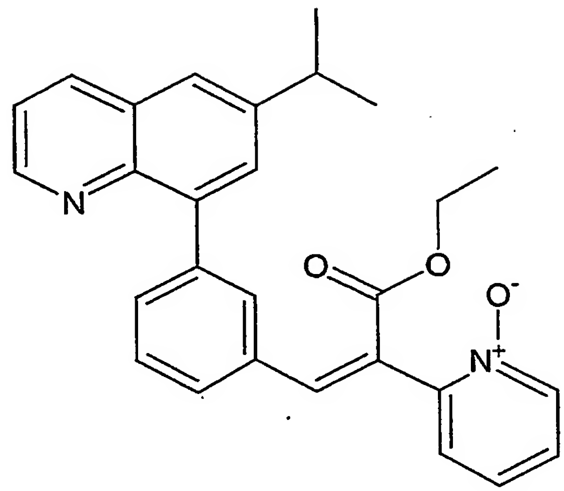

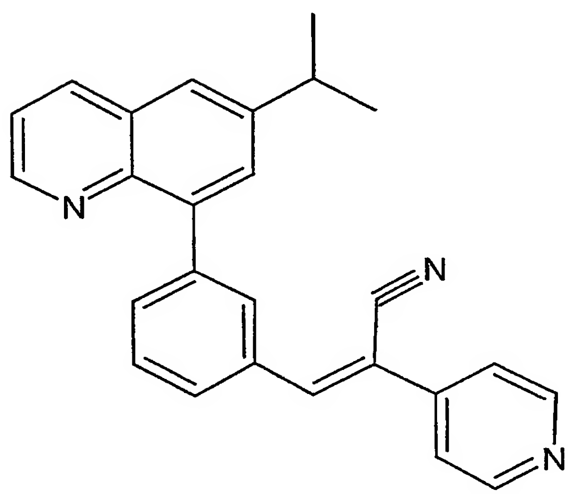

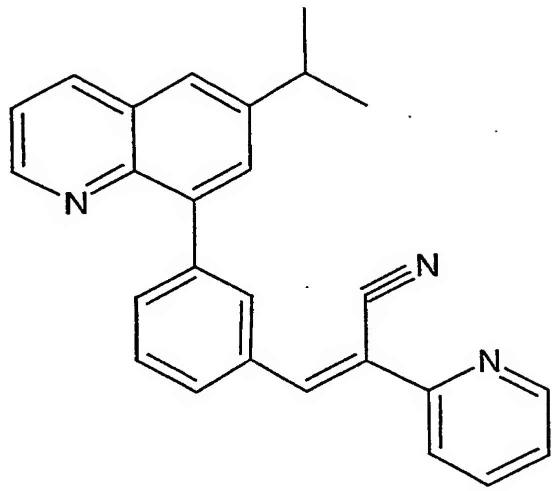

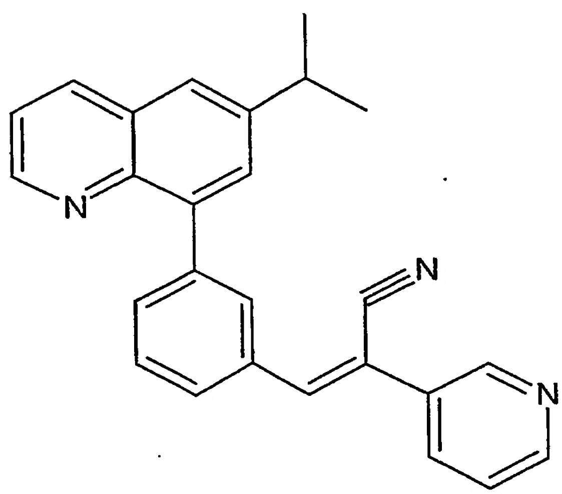

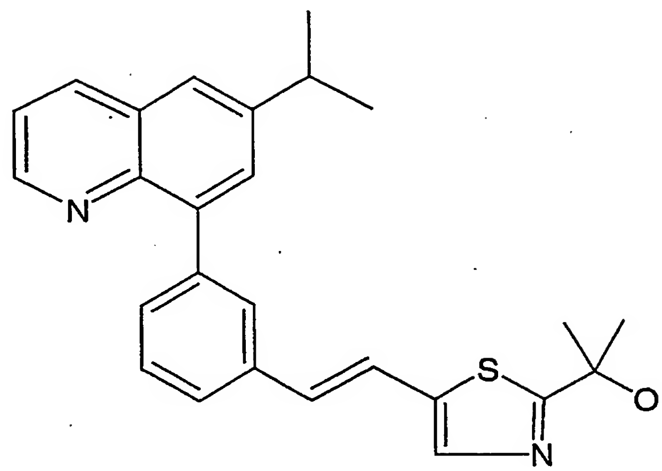
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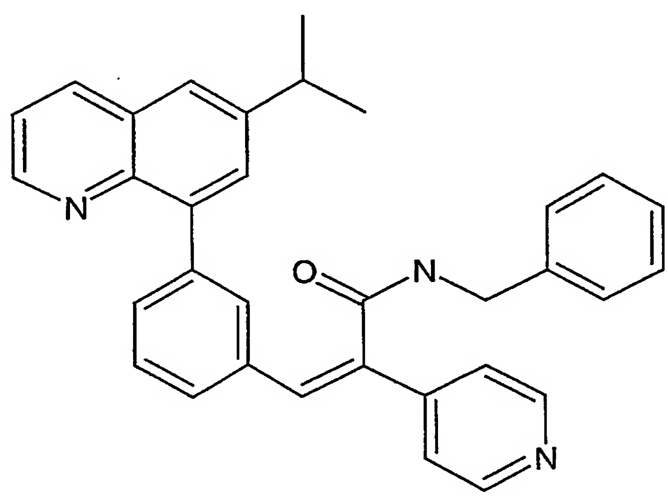
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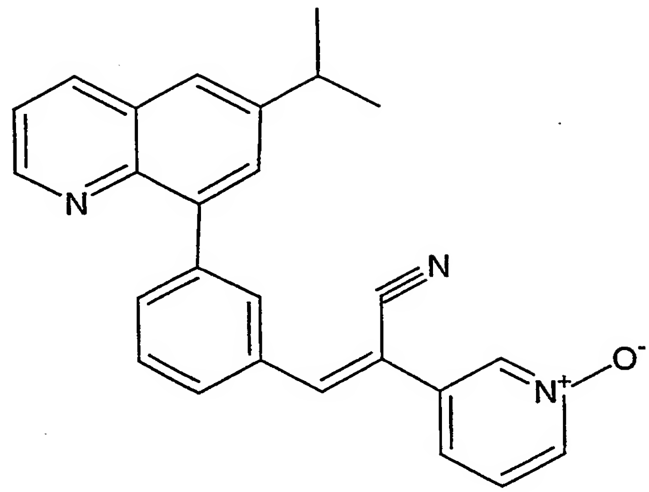

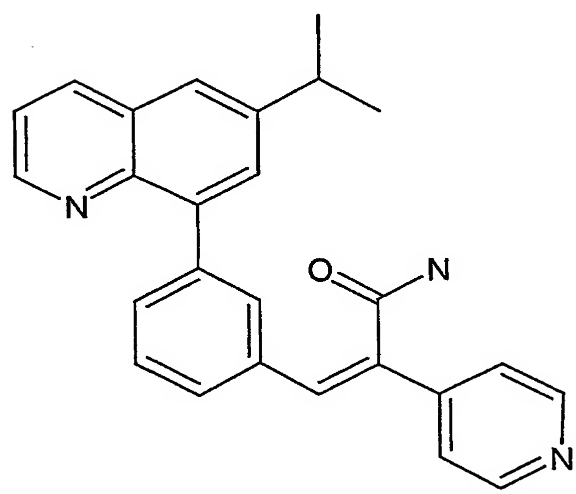

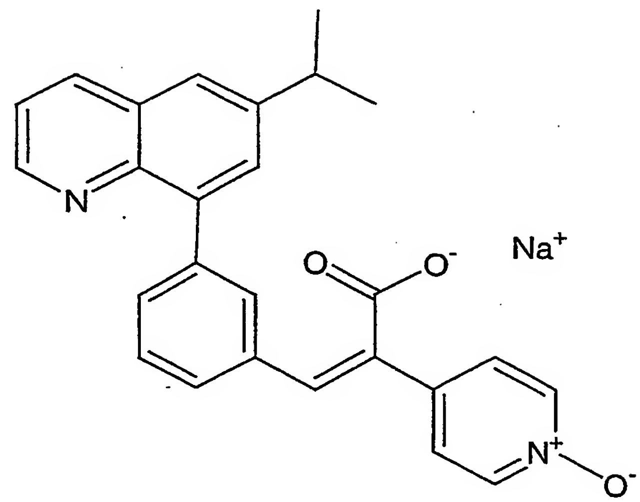
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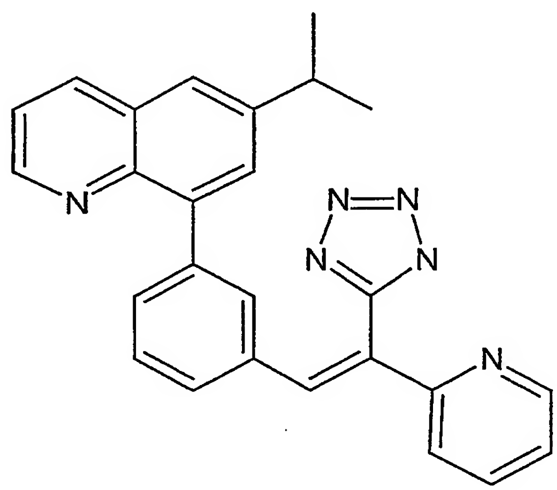
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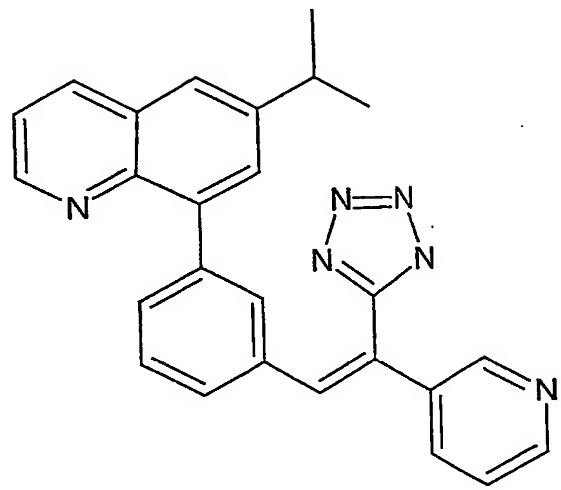
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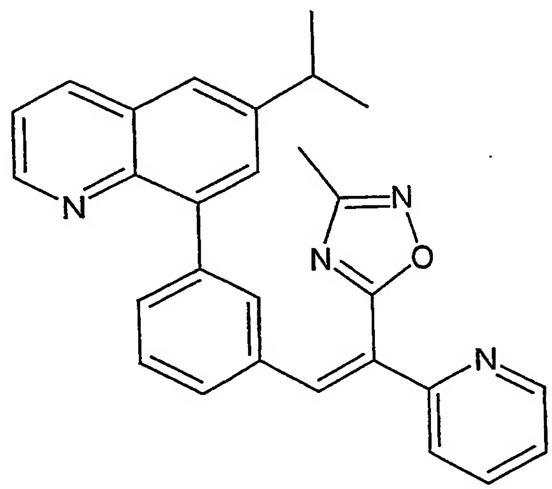
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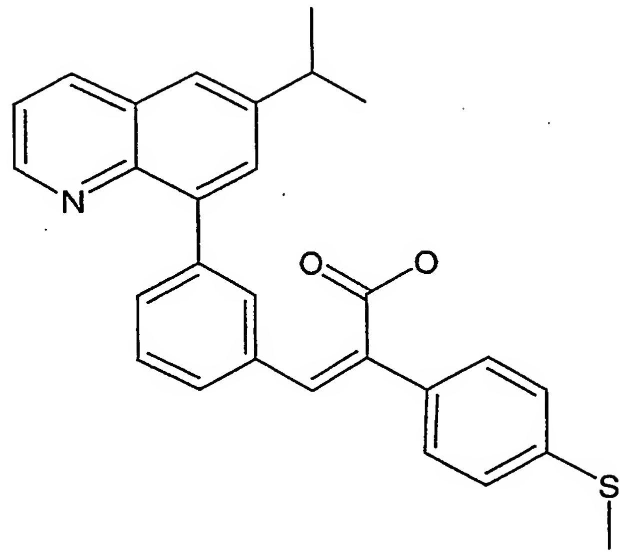
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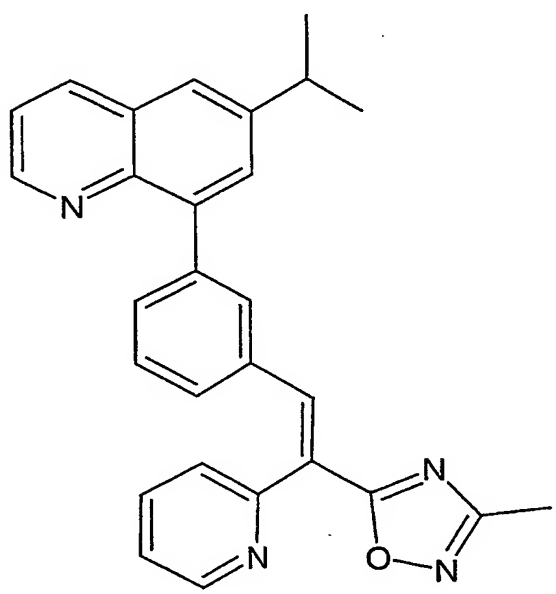
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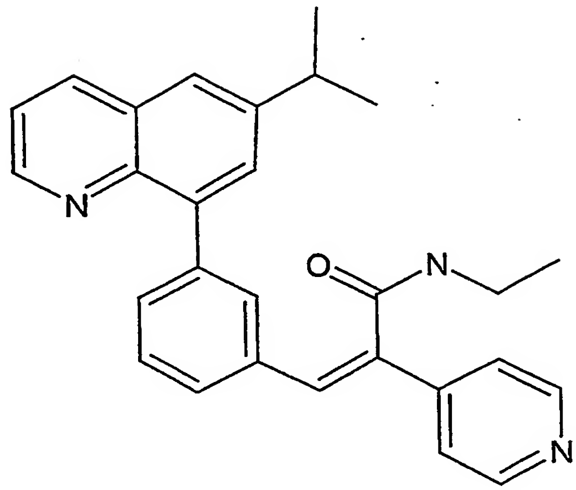

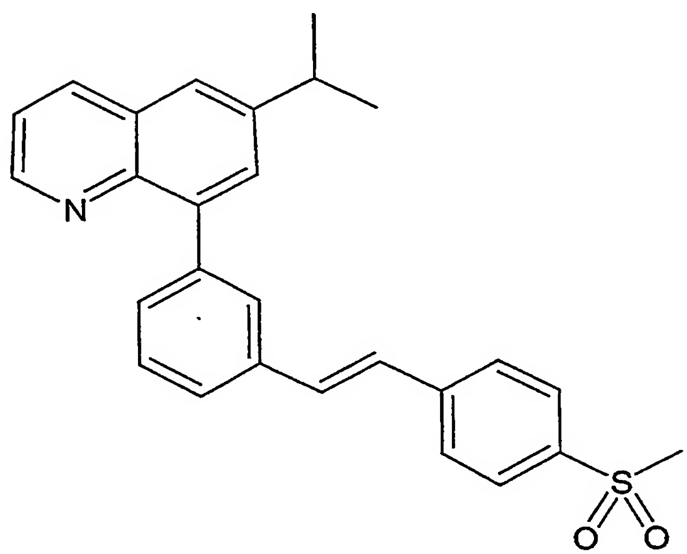

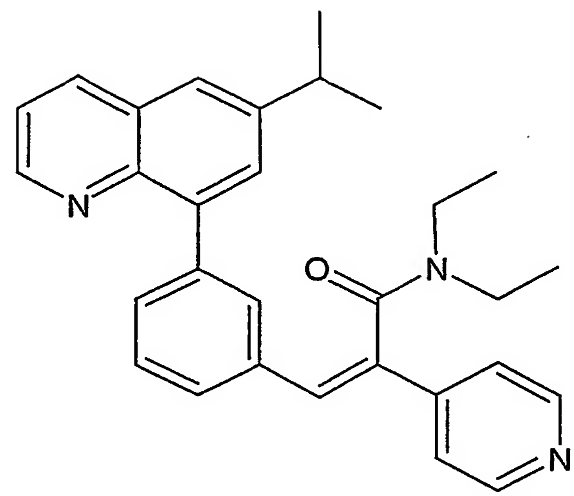

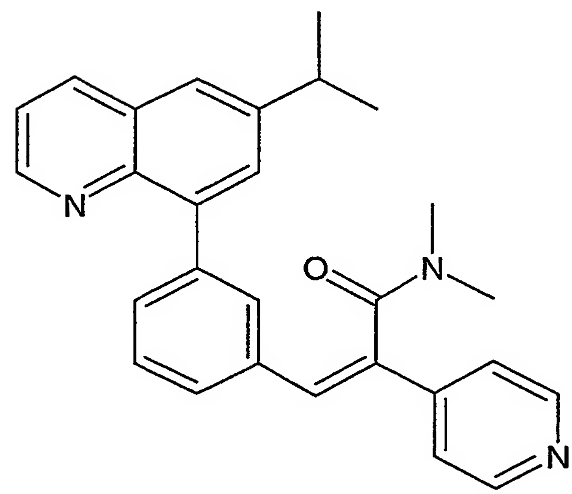

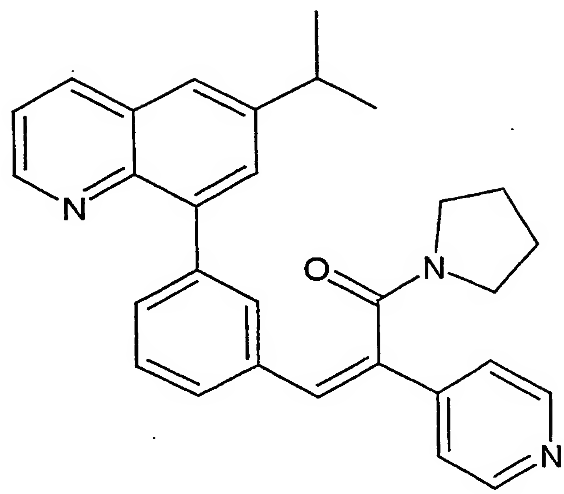

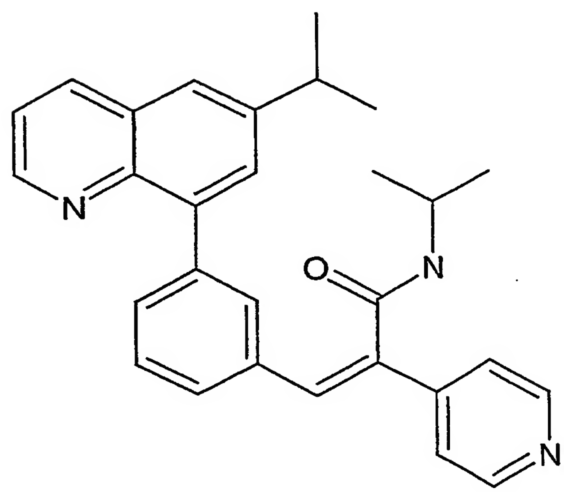

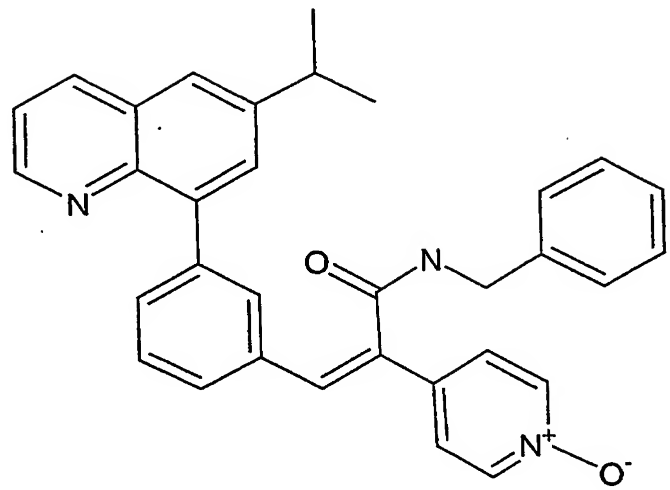

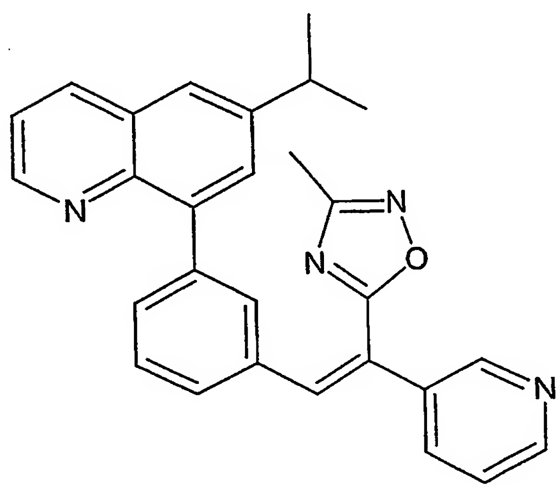

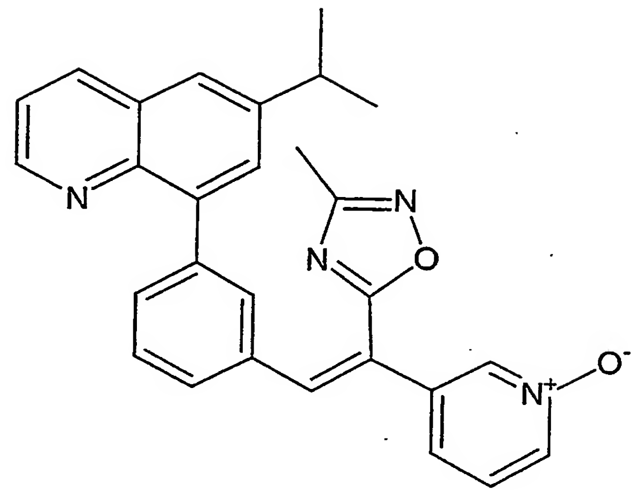

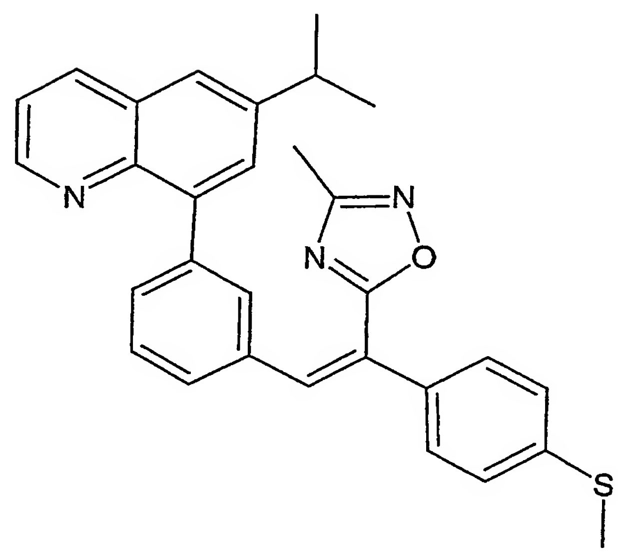

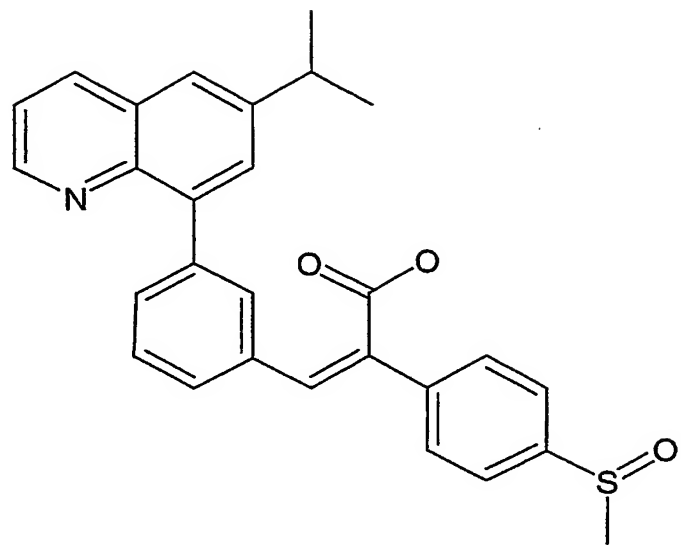

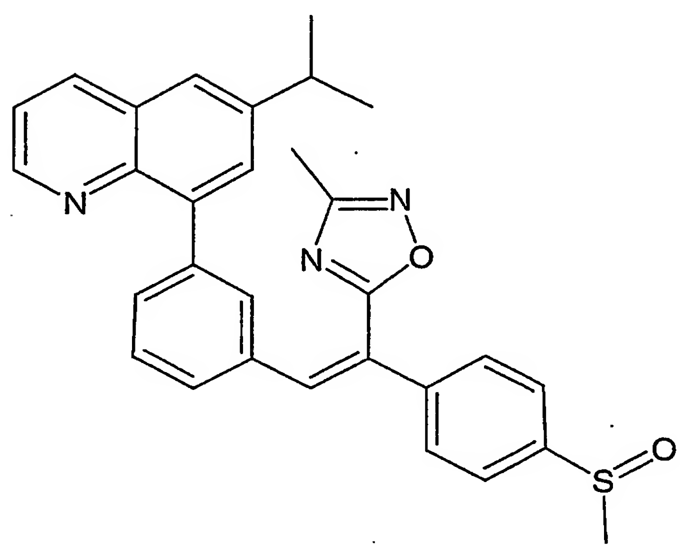

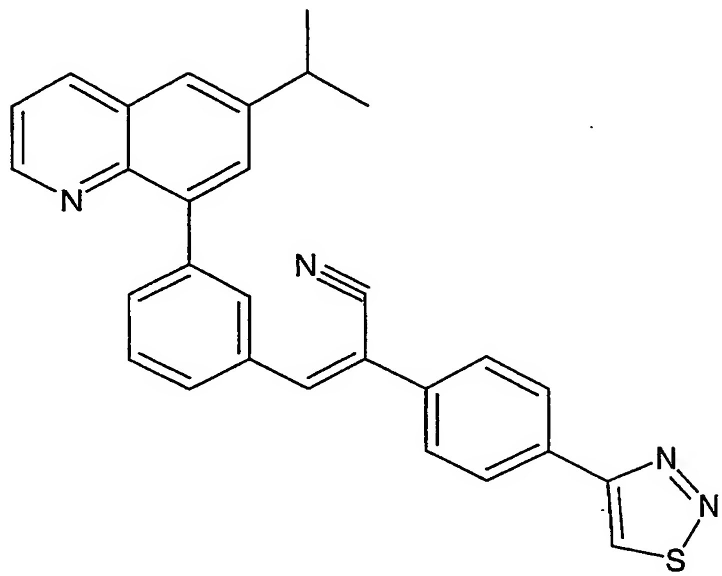
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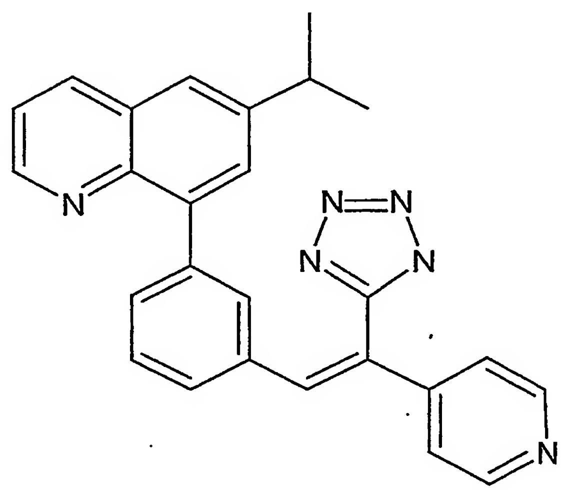
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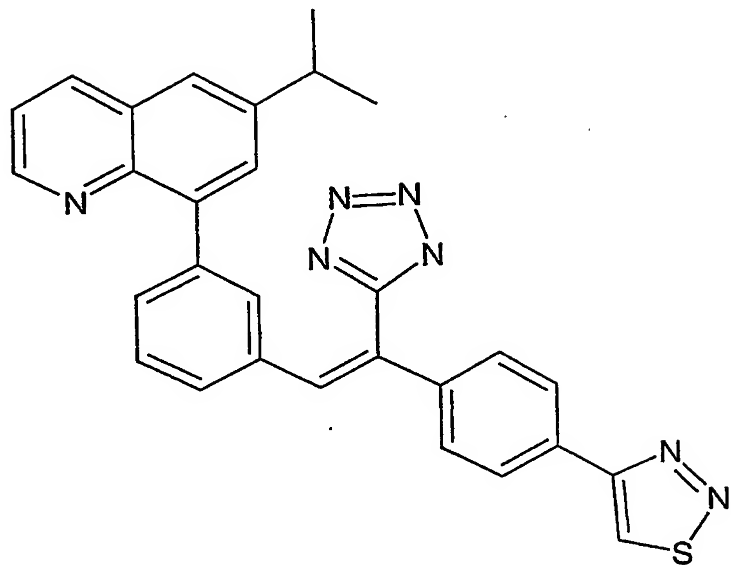

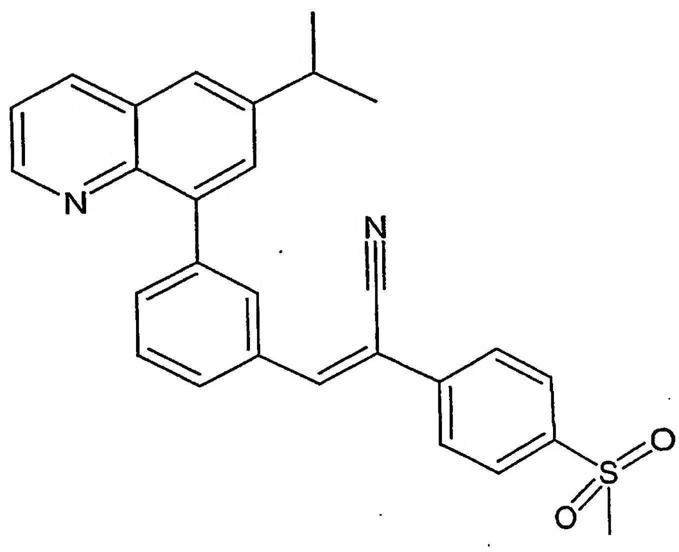

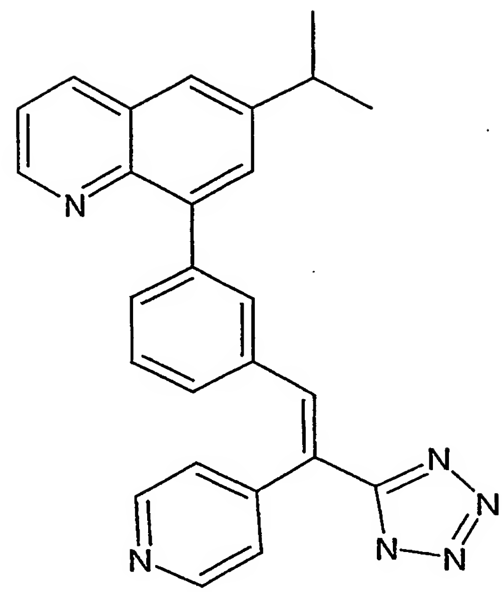

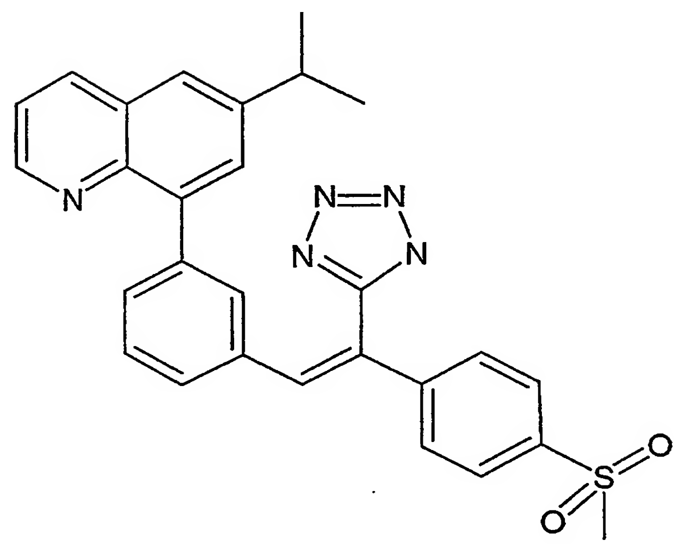

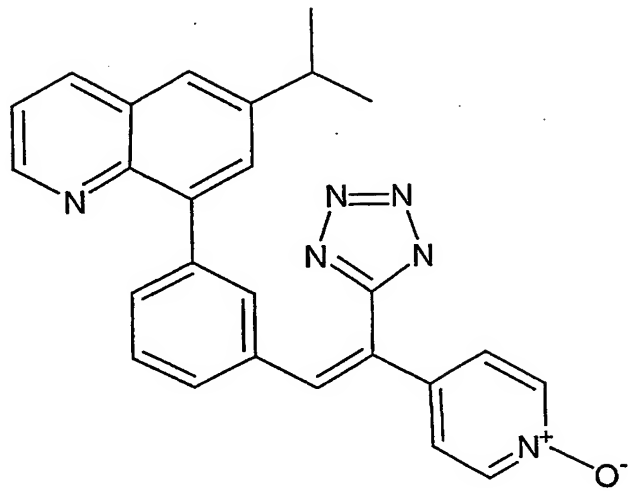
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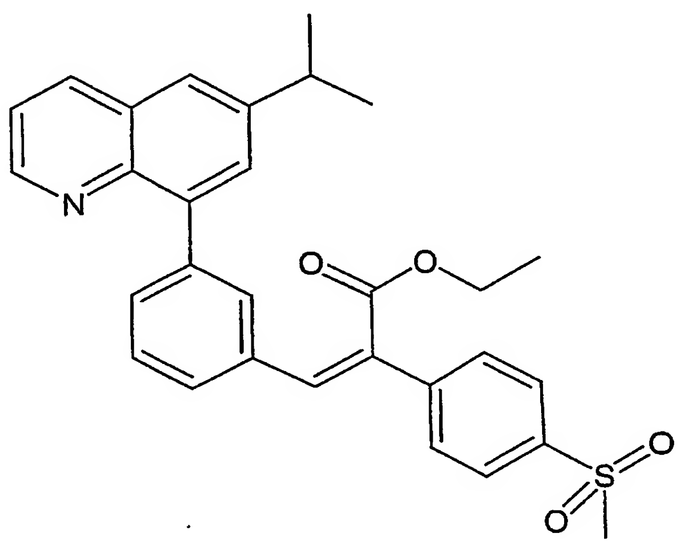
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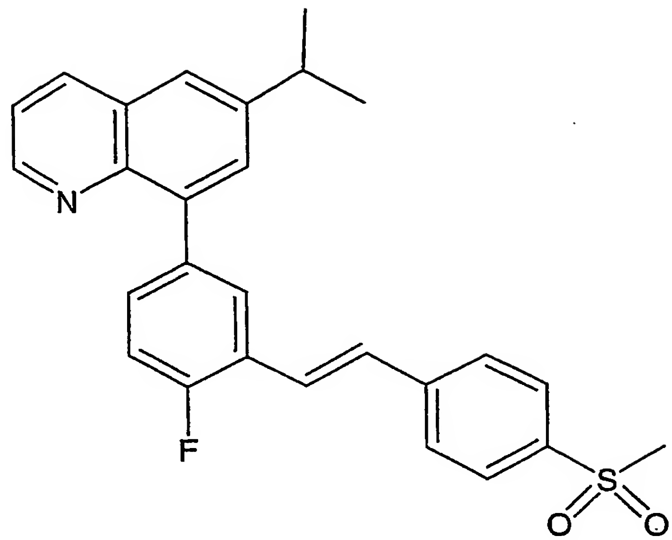
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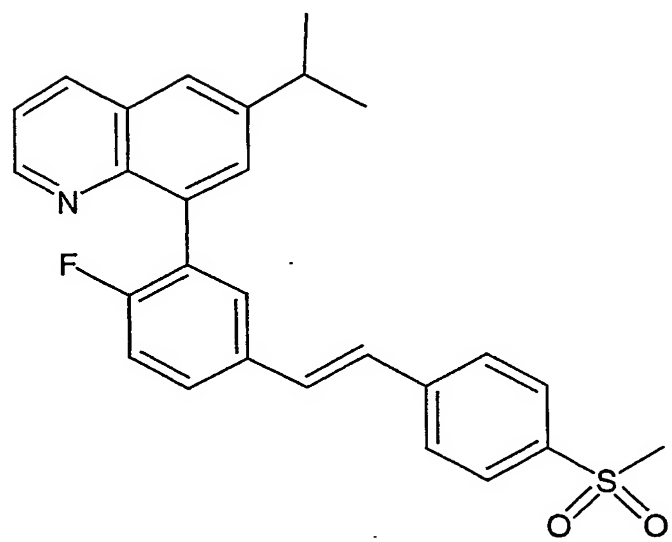
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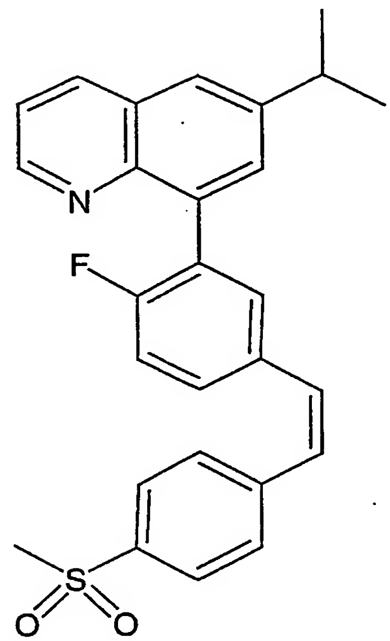

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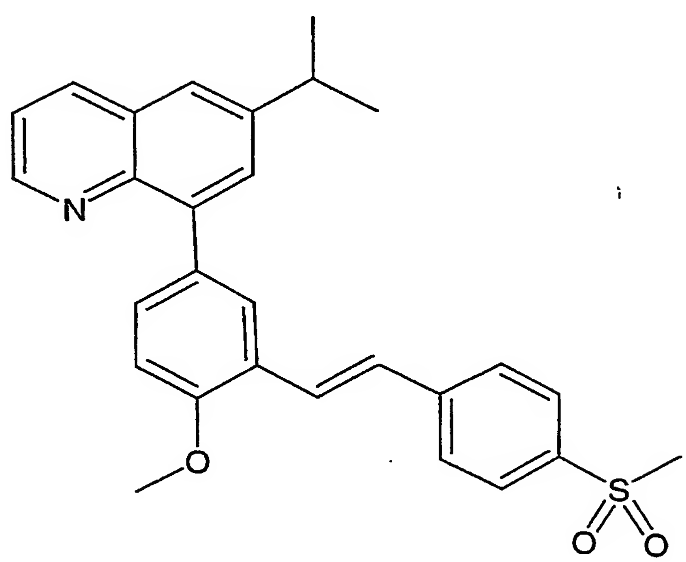

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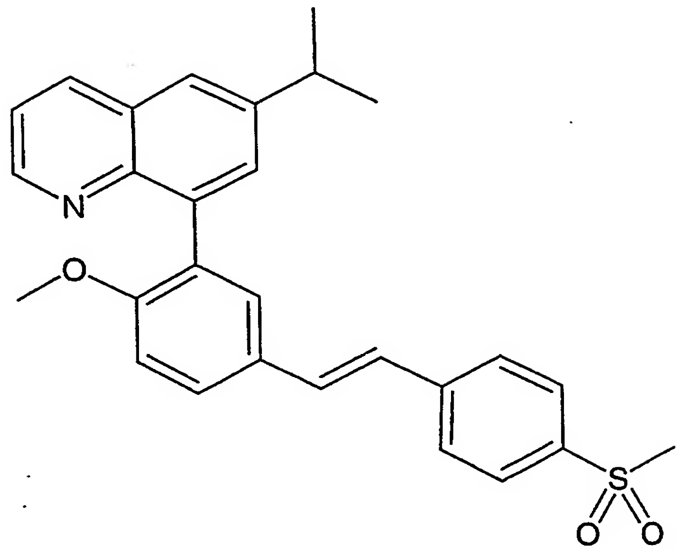

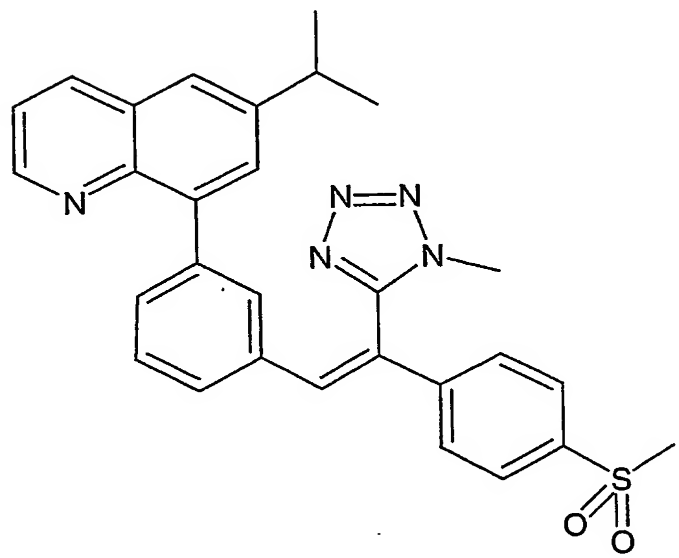

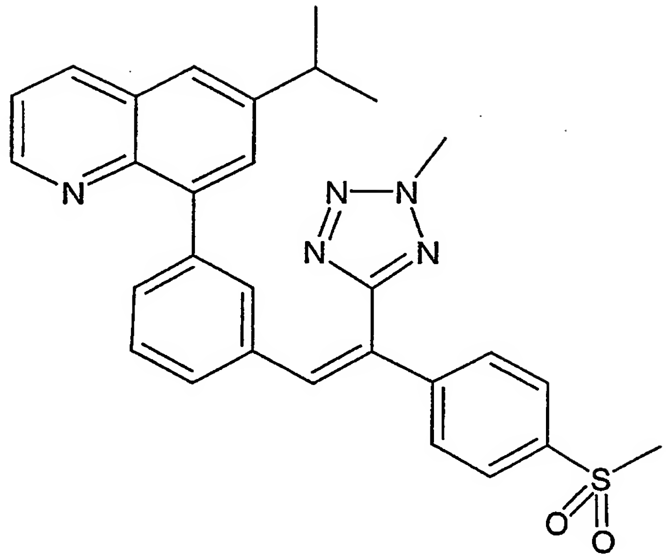

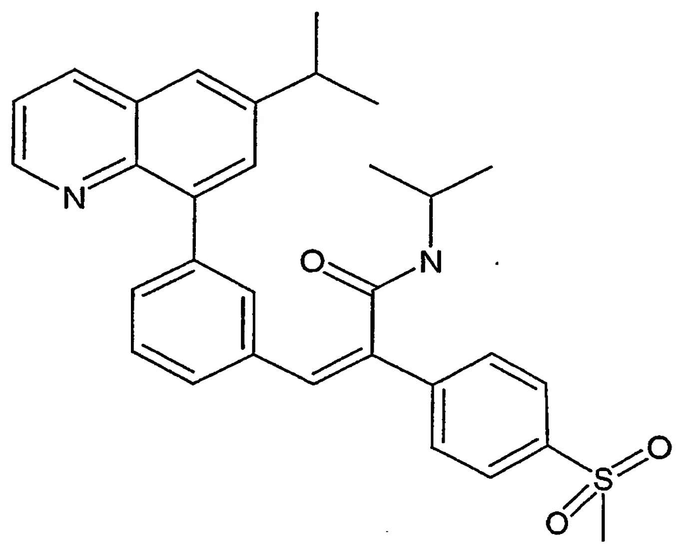

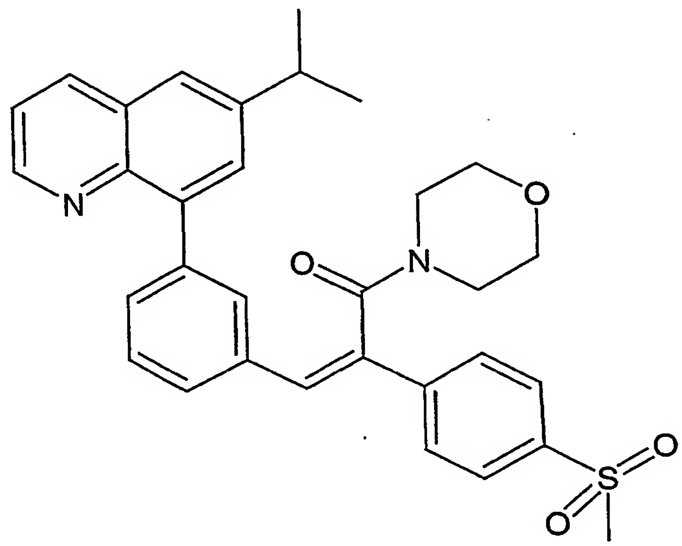

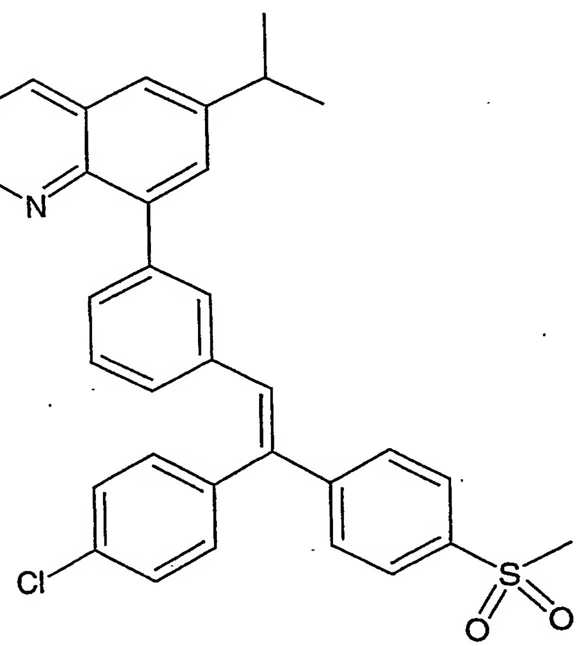

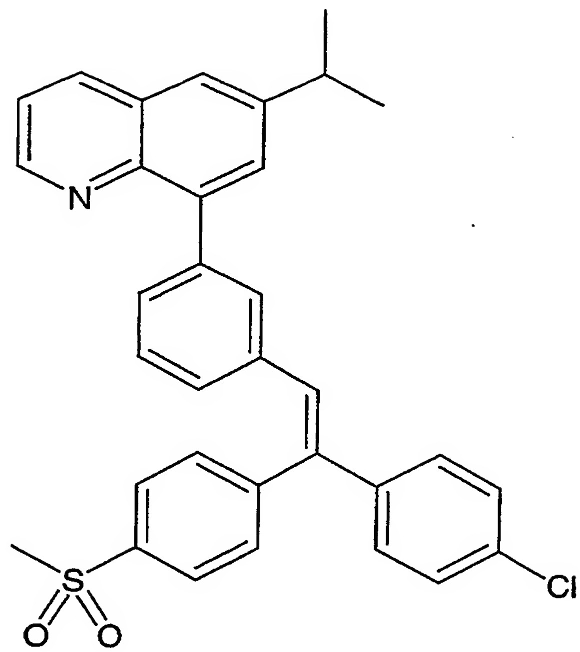
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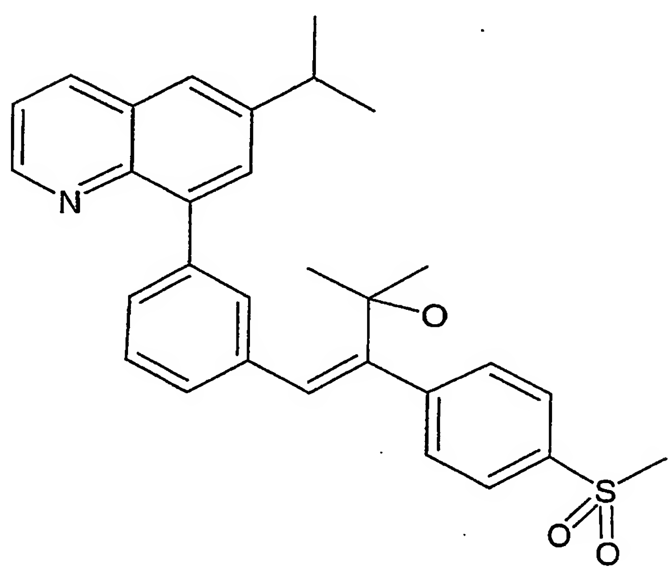
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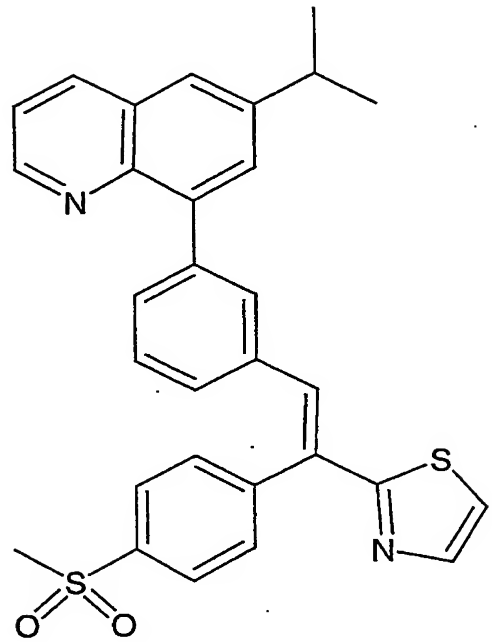

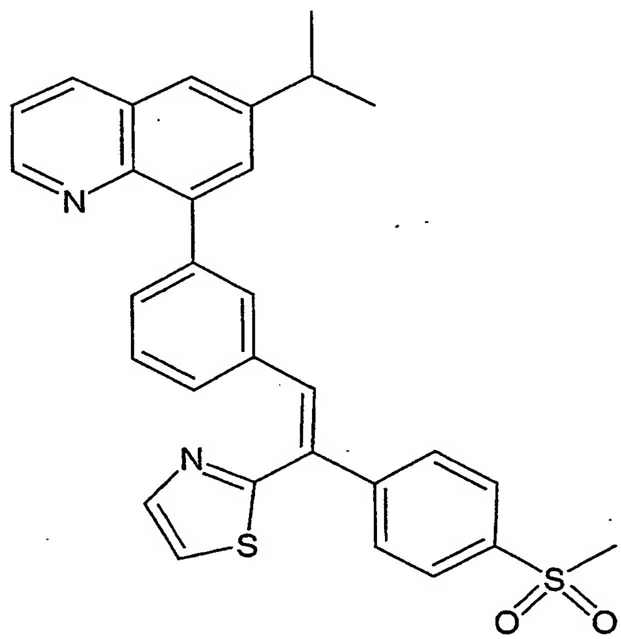

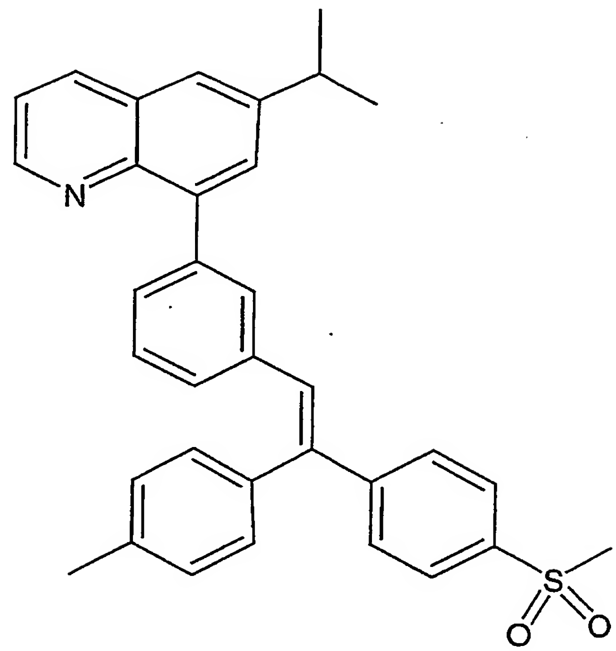

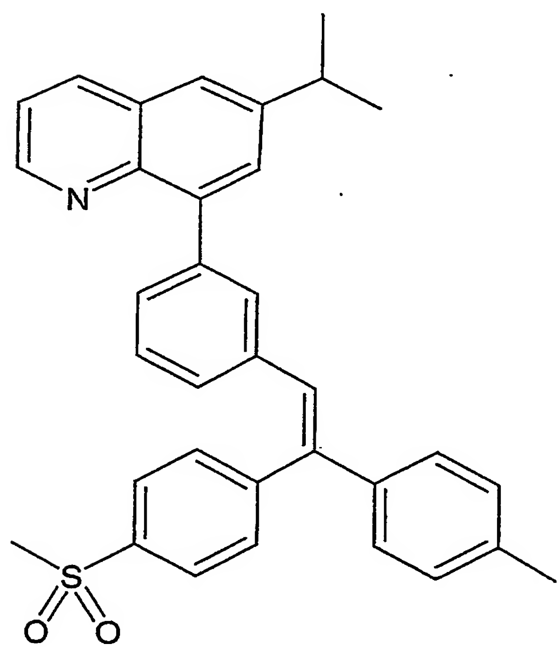

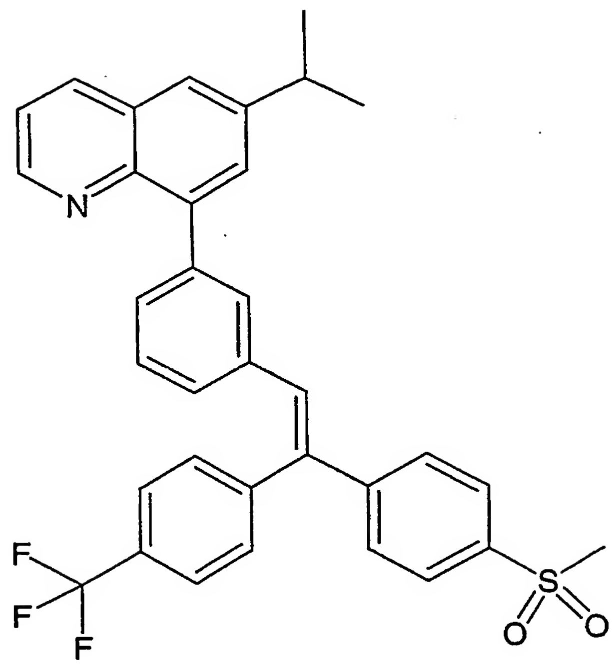

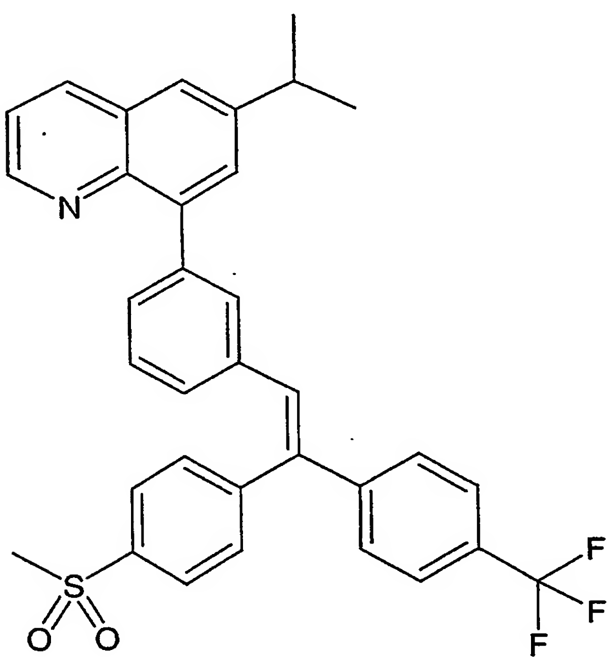

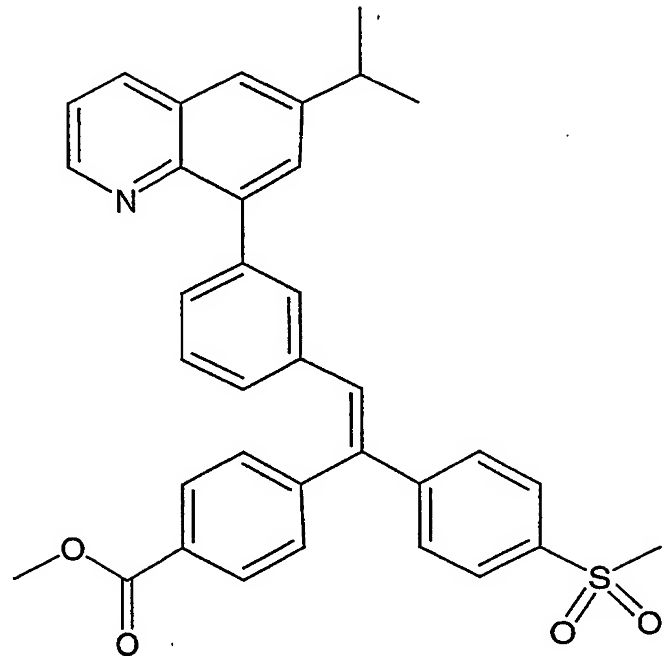

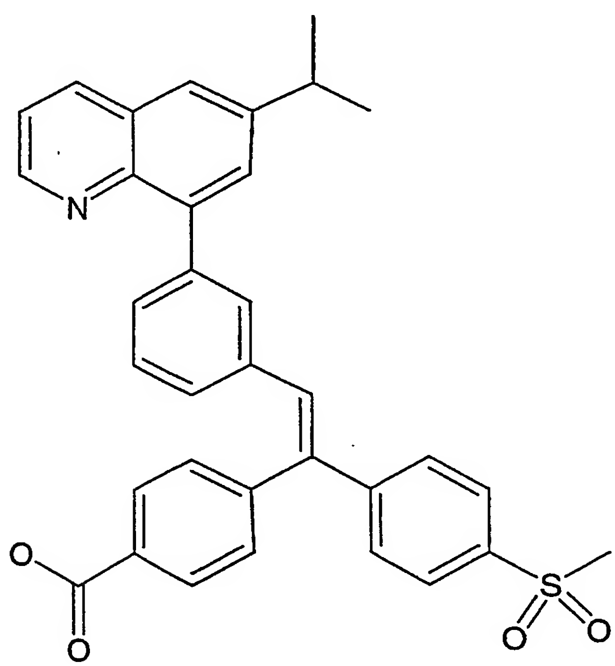

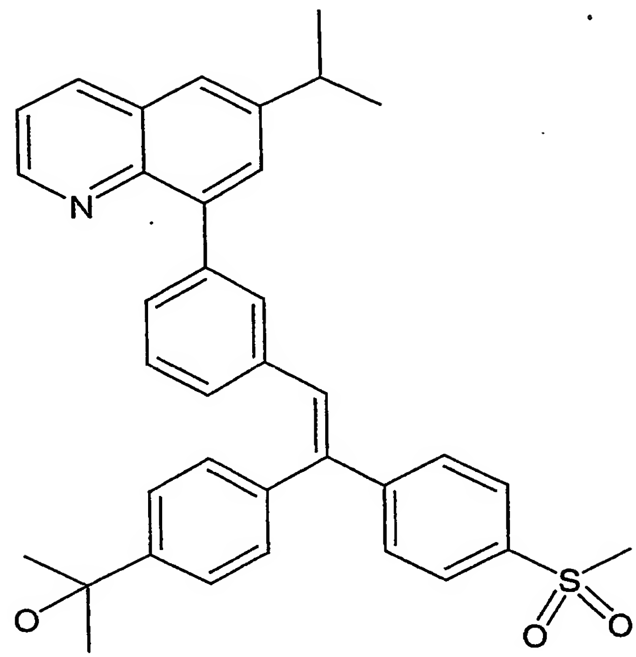
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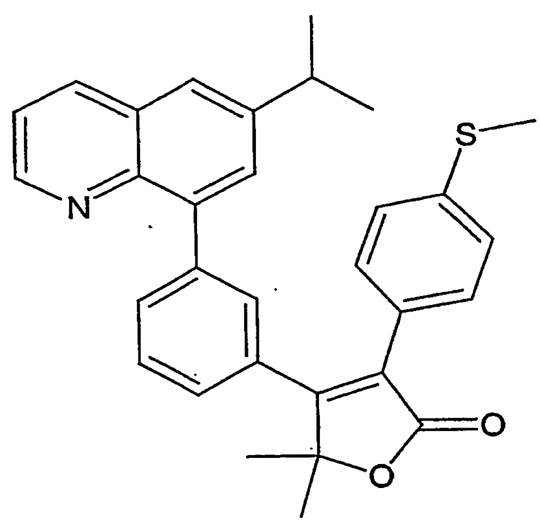
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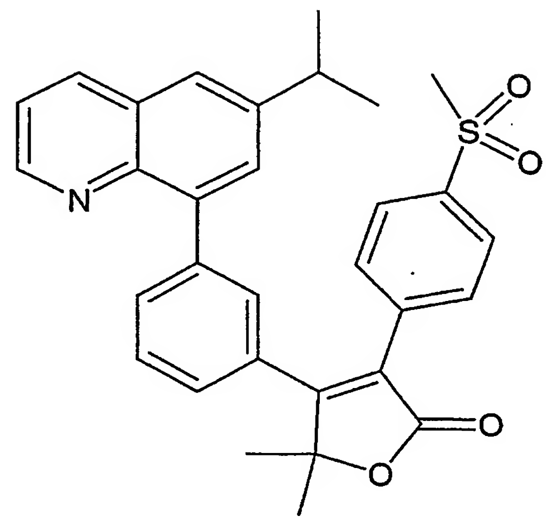

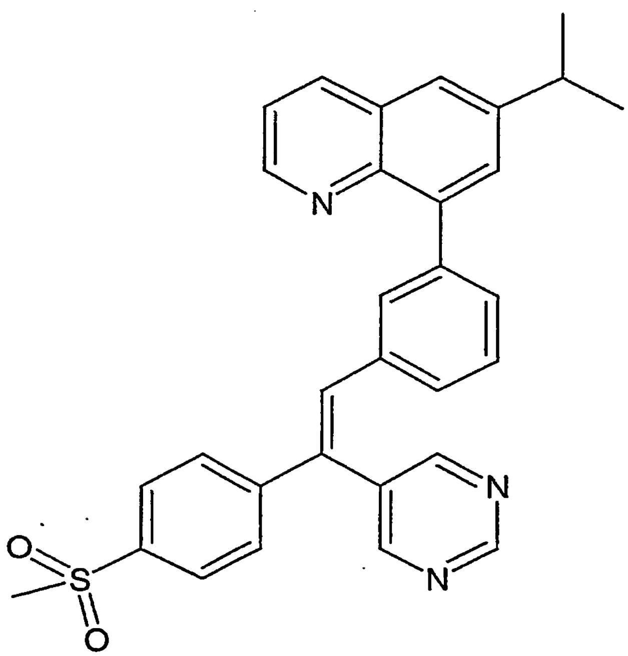

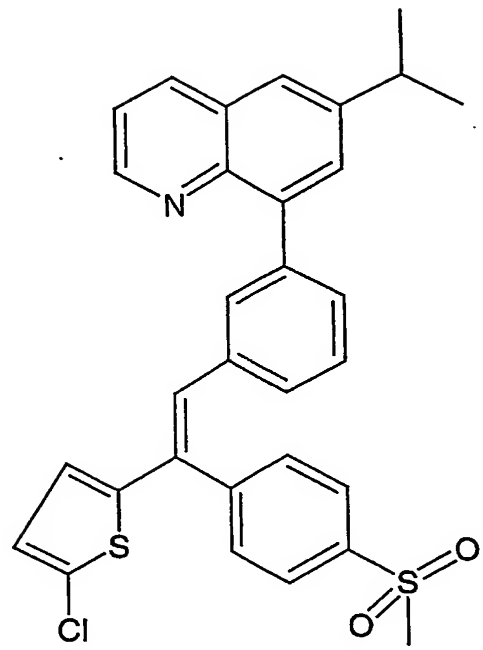
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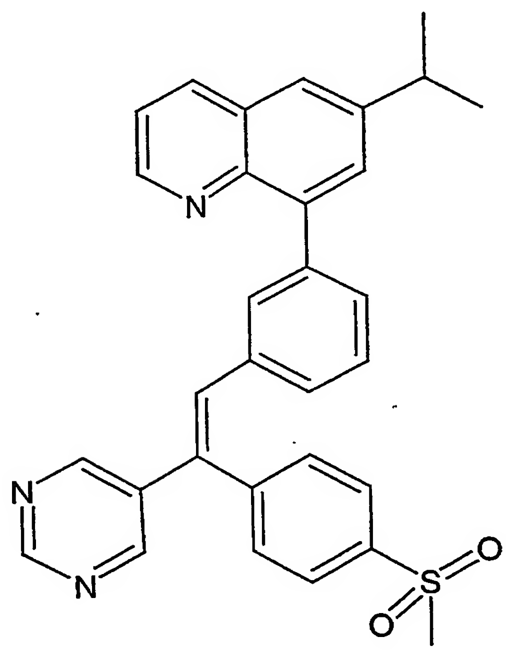
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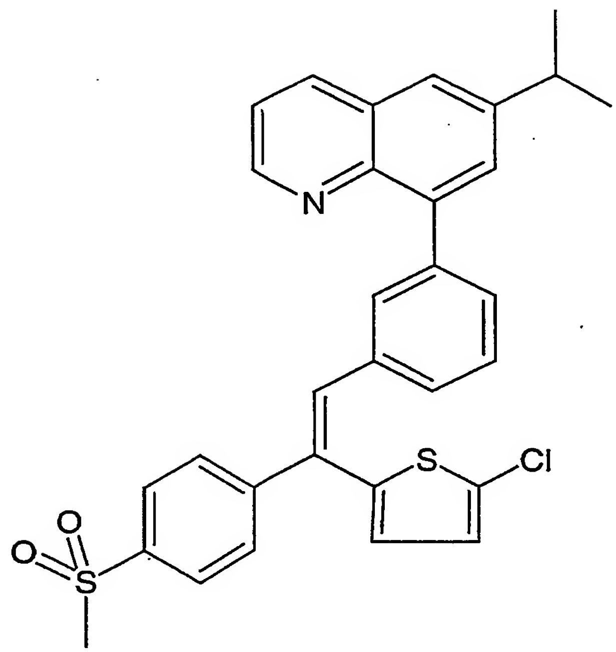
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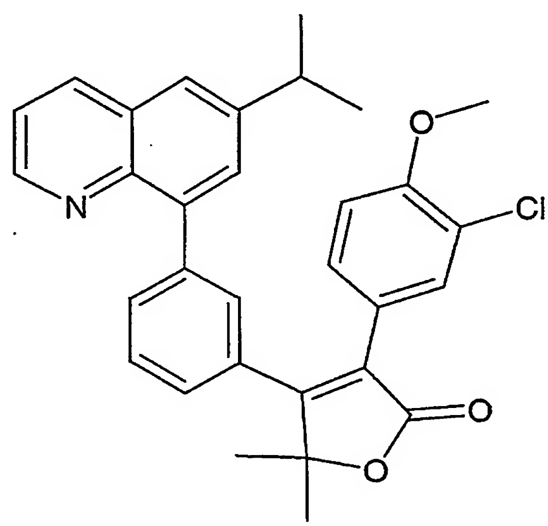
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